# PSYCHOSOMATIC DISORDERS IN CHILDREN *

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PSYCHOSOMATIC medicine has been called a scrap-bag and a junk-heap. It has been condemned as old and stale, and extolled as new and revolutionary. With all these terms we may agree: it depends on what psychosomatic medicine is taken to mean.

At the beginning of the last century Caleb Parry of Bath, who described Graves' disease before Graves did and recognised Hirschsprung's disease before Hirschsprung was born, wrote: "It is more important to know what sort of patient has the disease, than what sort of disease the patient has." It has been claimed that psychosomatic medicine is this way of thinking, with the patient rather than the disease as the prime consideration; but, though admirable, this broad definition should embrace the whole of medicine. Some prefer to limit the term psychosomatic to those disorders, presenting with bodily symptoms or disturbances, in which psychological factors play a primary part. It is this type of disorder which I shall discuss.

Perhaps one should say also what psychosomatic medicine is not. It is not a specialty. We might, somewhat cynically, infer that it cannot be a specialty, because its language is understandable in all branches of medicine; and also because, as the subject advances, its discoveries are unostentatiously woven into the texture of general medicine.

In most illnesses both physical and emotional factors are concerned. When we are in doubt, what should decide us to term a disease psychosomatic? I think the decision is not so much a theoretical as a practical one. When the term is used it should be helpful to the doctor, not only in diagnosing and treating, but also in understanding the disorder in the individual patient.

## The Background

Modern medicine began to develop in the climate of the Industrial Revolution, which ushered in a profound change not only in material conditions but also in men's minds. It was this change which potentiated the scientific approach to human affairs. Medicine benefited accordingly, but suffered also one of the disadvantages of this new approach: it became, and still tends to remain, excessively mechanistic. The medical profession has encouraged a garage-mechanic mentality. We look for "the part" which has gone wrong—and sometimes, it must be admitted, we find it, remove it, and occasionally even replace it with a spare part. This attitude has been encouraged by the undeniably important advances made by physiologists, studying the functions of artificially isolated organs but showing little interest in the interrelationships of organs in the integrated individual. To this generalisation Claude Bernard was a brilliant exception: it was on such grounds that, while appreciating the importance of Pasteur's work, he was concerned with its restrictive effects.

The discoveries of bacterial causes of disease, of deficiency diseases, and the like, essential though they were to the advance of medicine, enhanced the mechanistic approach. An over-simplified picture of disease resulted. Syphilis is due to the *Treponema pallidum*, but the life-history of the spirochæte gives neither the beginning nor the end of the story. The solitary bachelor, undernourished both physically and emotionally, may develop scurvy; but the fact that he is ill is not to be explained simply in terms of the biochemistry of ascorbic acid. In the effort syndrome no amount of cardiac investigation could reveal the cause of the disturbance.

Nature appears simple only to the simple. Nature is complex, and so is Man. The notion that there is a single, simple cause for each disease is so over-simplified as to be misleading: in each patient many factors play a part. Nor is a pattern of response unique to any particular stimulus. A fundamental advance which psychosomatic medicine has made is to show that the same patterns of response may be provoked in the body by widely different agents—whether they are physical, chemical, bacterial, allergic, or psychological. An example is found in the nose, where tobacco smoke, nasal drops, infection, pollen, or emotional disturbances can all provoke vasodilatation, hypersecretion, and consequent occlusion. Similar examples, affecting organs or systems, are common in clinical practice.

How much more rational medicine becomes when it is appreciated that there is nothing unique or mysterious about the patterns of response in psychosomatic disorders; and, to go a stage further as the result of careful observations, that many psychosomatic diseases are exaggerations of reaction patterns which occur in healthy individuals.

## The Doctor

*A dissertation on the influence of the passions upon disorders of the body* (1788) gained for William Falconer the Fothergillian medal of the Medical Society of London. Dr. Lettsom, presenting the medal, wisely said: "Every practitioner, therefore, who studies the honour of his profession, and the happiness of his patients, should sedulously endeavour to cultivate an acquaintance with the anatomy of the mind, as well as that of the body".

The clinician who successfully practises psychosomatic medicine must be a good all-round doctor. We take it for granted that he will know how the body functions. He should certainly take a pride in being "good at physical signs", but he must not let them shut him off from the rest of reality. He must be interested in how the mind works, and he may find it natural to believe, as modern philosophers do, that the working of body and mind cannot be separated.

One of the great difficulties in being a good all-round doctor is lack of time—time in which to find out as much as possible about the patient. Unfortunately, when time presses the doctor tends to take up his pen. How much easier and quicker it is to give the child with "growing-pains" an aspirin preparation—looking like melted ice-cream and tasting of raspberries—than to find out why he is emotionally insecure. Not 1 child of every 20 children with growing pains has organic disease; but some are kept by us from school, some are put to bed, and many are dosed.

* Based on an address to Southampton Medical Society, Jan. 14, 1959.

If, in consequence, they come to look at life through distorting spectacles, it is we who are partly at fault.

### Physical Disorders

We are at fault also by reason of the traditional medical training. As clinicians we have been trained to seize on an abnormal physical sign almost with a feeling of relief. A spot, a lump, a sound—an abnormality which can be seen, felt, or heard—affords the same sort of satisfaction as playing games. The pitch has been marked out and the rules are known; the linesmen are our technical colleagues (in the laboratory or X-ray department); and the referee is the morbid pathologist.

But practitioners do not need reminding that a significant physical abnormality can be found in only a small proportion of the patients we see, and that some of those we do find are misleading, inasmuch as they are not causally related to the patient's disturbance.

With this background, if we find no obvious cause for the patient's trouble, it is tempting to set out on a witch-hunt of physical investigations. We see very clearly the dangers of diagnosing a nervous or functional cause in the emotionally disturbed patient who is suffering from a brain tumour, lead poisoning, or the cœliac disorder. We see less clearly the dangers of inducing or confirming a fear of disease, or of promoting the symptoms of disease, with the doctor himself acting as " a pathogenic agent, in his well meaning but never ending efforts to find a physical cause " (Weiss 1947).

### Diagnosis

There are three complementary aspects of psychosomatic diagnosis:

First is *negative evidence* adequate to eliminate organic disease. The evidence should be adequate; but what William Penn called " a wantonness in inquiry " is a sign of medical immaturity, is unnecessary, and may be harmful.

Second is *positive evidence* of emotional disturbance. Often it is found, too, that symptoms recur when stress recurs. Most of us were not trained to obtain this sort of evidence; we need to cultivate understanding and to learn to listen, and in this we can learn a great deal from our psychiatric colleagues.

Third, treatment, not of the symptom, but of the emotional disturbance or, better still, of the stressful situation which underlies them both, often improves or removes the symptom. At the same time it may gratifyingly improve the patient's attitude to life and the problems with which he has been contending badly. For most of us non-specialists this sort of treatment involves taking a personal interest, not limiting ourselves to the superficial, listening patiently, explaining and reassuring, and offering sensible guidance. It is usually effective, but a small proportion of children with psychosomatic disorders will need treatment by a psychiatrist with a special interest in this age-group.

### Some Childhood Disorders

It is surprising that the study of psychosomatic disorders in children has been so neglected; possibly this neglect is due to our natural preoccupation with the fast-moving physical events in early life. Yet, compared with the adult's, the child's world is smaller in time and space, and easier to explore. Moreover, his emotional problems often lie near the surface where, if we know what to look for, they can be unearthed without much digging.

I can discuss here only a few of the psychosomatic disorders of children, and merely mention that even in some illnesses not included under this heading psychological disturbances may play an important and even decisive role. An example is diabetes mellitus, in which anxiety, fear, or rage may provoke so severe an acidosis that the child's life can be endangered. Another is epilepsy, in which an emotionally disturbing situation may produce an " escape " from drug control and a startling increase in the number of fits.

*Recurrent Pains in Childhood*

Recurrent pain is the commonest psychosomatic disorder of childhood after infancy, as surveys of unselected schoolchildren indicate (Apley 1958).

" Little bellyachers " are especially frequent, though only about 1 in 20 has an organic disease which will satisfactorily explain the symptoms (Apley 1959). Taking as criteria the occurrence of at least three attacks of pain, severe enough to modify the child's activities or appearance, it was found that among unselected children questioned at school 1 in every 9 was affected (Apley and Naish 1958): not all of them are taken to their doctors, though they are more likely to be if they are " only children ". Before conclusions were drawn about them they were compared against children without pains. No valid differences were found physically or intellectually but from the emotional aspect there were obvious and significant differences between the two groups.

Children with recurrent abdominal pain, with no organic cause, often have characteristic personality traits (in general they are indrawn and overconscientious); and usually they show evidence of emotional disturbance. Both these features, it is important to note, often precede the pains, and cannot therefore be attributed to them. In half the families of children with abdominal pains some other member of the family, usually a parent, has a history of similar pains, a proportion many times higher than in controls (Apley and Naish 1958). A high proportion of the families also have disorders such as peptic ulcer, migraine, and nervous troubles.

I will not go into detail about children with headache or limb pains, but the findings are similar to those in children with abdominal pains (Apley 1958): only 1 patient in about 20 has organic disease; a high proportion have emotional disturbances; and many of the families have similar pains and nervous disorders.

We often tell parents that their child " will grow out of it ". Is this true? Does it matter if we do not call these disorders psychosomatic, and in consequence they are treated incorrectly or are not treated at all? I will suggest an answer to these questions from the studies of children with abdominal pains (Apley 1959):

Of 30 children with recurrent abdominal pain who were followed up after eight to twenty years, 9 were completely symptom-free. Of the 21 with symptoms, 12 had continuing abdominal pain (usually with other symptoms), and among all 21 other symptoms were present as follows: typical migraine in 3, recurrent headaches in 15, nervous disorders in 13.

In this follow-up series the figures for abdominal or other pains and for nervous disorders in later life were many times higher than those in another group of children, followed up after a similar interval, who had attended hospital with other and minor complaints.

Clearly many of the children with recurrent abdominal pain do not grow out of it, or, if they do, develop other significant disturbances. Correct diagnosis and rational treatment early in the course of this psychosomatic disorder would surely prevent much unnecessary suffering.

*The Periodic Syndrome*

I look on recurrent abdominal, head, or limb pains as part of a wide spectrum of disorder—the periodic syndrome—of which other components are vomiting and fever. The different components may occur singly, as in cyclic vomiting or recurrent pyrexia, or together; though the combinations vary from case to case, or from time to time in any individual. Thus, vomiting in infancy tends to be superseded by abdominal pain later in childhood; bouts of fever tend to become less pronounced as the child grows up; and abdominal pain is often replaced by recurrent headache or migraine in adult life.

It is difficult to conceive of any purely physical cause to explain such manifestations, recurring over many years, though many have been postulated. " Grumbling " appendicitis, mesenteric adenitis, abdominal epilepsy or migraine—these are " names men use, to cheat despair ". The more critically such supposed causes are examined the less convincing they appear, with rare exceptions; but when we widen the scope of our inquiries the evidence for psychosomatic disorder becomes very convincing.

*Asthma*

Many will agree that years of research and clinical observation have minimised the overriding importance which was previously attached to allergy as a cause of asthma. Some of us have been driven to believe that the treatment of allergy in asthmatics is effective mainly, if not entirely, as a vehicle for suggestion. There is surely no single cause for asthma; many factors—hereditary, constitutional, and acquired—must be concerned. In a predisposed individual the response we call asthma may be provoked by various stresses—allergic, infective, or emotional. The important point is that allergic or infective stresses are less likely to produce asthma, or may completely fail to produce it, when the patient is emotionally stable. If he adjusts himself emotionally, with or without medical help, though the skin reactions to his allergens may remain positive, exposure to them may no longer provoke asthma (Gerard 1946).

When we send seriously crippled asthmatic children away from home—to Switzerland (though the Swiss also suffer from asthma), to special schools, or to convalescence —what are we sending them away from? It is surely from an " atmosphere " in which allergy and infection are less important than emotional tension. It has been said that the asthmatic child's commonest allergy is to the mother, poor woman, or rather to her subconscious attitude. In the battle of personalities which takes place below the surface, the child may be the victim. Asthma is one of the psychosomatic disorders which cripple and may kill.

At present we may try to modify the physical reactions by drugs, including steroids; or we may bypass the problem by sending the severely afflicted child away. But perhaps one day we shall know enough about the child-parent relationship in asthma to treat or educate the parents before the child develops asthma, or even before he is born. Antenatal mental-health clinics might come to play as important a part in the nation's mental health as do the antenatal clinics of today in its physical health.

*Feeding Problems*

Mention of antenatal clinics brings one naturally to problems of feeding. With the older child, or adult, when the doctor is in doubt or in haste he tends to change the medicine: with the infant he changes the milk. Yet, if we can find time to question not only our patients but also ourselves, we must surely admit that feeding difficulties are rarely produced by any particular brand of the better-known milks—a term which still includes breast-milk! " Changing the brand " is another example of the garage-mechanic mentality. Petrol or milk—if one brand does not seem to give smooth running, good acceleration, and a healthy exhaust, we are tempted to try another. But rarely, in the event, is the milk preparation at fault; and rarely is the baby at fault in the sense of being physically ill. On the other hand, it is certain that a large proportion of feeding problems not due to hunger —the commonest cause—can be solved by attention to emotional difficulties (Mac Keith 1955).

To use an electrical term, this is psychosomatic disease " in parallel ": the mother's disturbed psyche may produce physical (as well as emotional) disorder in the child.

The feeding problems of infancy are often an aspect of the rejection of food, but problems of over-feeding also arise. Even the best of mothers is liable to " mothermanship ": every ounce her baby puts on is a point up. Obesity and a feeling of insecurity may be associated: the older child may eat whenever he feels disturbed—a habit which often starts after an illness or separation. In children who are fat a familial tendency is usually apparent; one wonders how much this reflects a physical (endocrine) and how much an emotional predisposition, and how much it is just due to acquired eating habits.

*Some Sphincter Disturbances*

Long-continued diarrhœa, encopresis, constipation—in only a small proportion of children with one of these disorders is an organic cause found. It is, of course, important to detect gut infection or anal fissure, for example, in the early stages when they are most readily curable. But in most cases the history alone can eliminate the possibility of organic disease, and the still too-common methods of treatment—by diet, drugs, suppositories, and enemas (with the child forcibly held down for their administration)—are irrational and harmful. The underlying stress and emotional disturbance should be treated instead.

Enuresis may be an index of insecurity in the child, and should then respond to explanation and reassurance and the amelioration of the underlying cause. But I do not believe that all enuresis is psychosomatic. In some children it seems to be a form, not of psychological disturbance, but of delayed maturation, which may be familial. In such cases the danger is that if the child and his symptom are mishandled, emotional stress may be superimposed: the enuresis of immaturity may lead on to the enuresis of insecurity.

**Treatment**

I have hardly touched on treatment, but the essential first step in any rational treatment is to make the correct diagnosis, and in psychosomatic disorders this is too often overlooked. When psychosomatic disorder is diagnosed, treatment is based on what should be standard practice in all medicine: to understand as much as possible about the patient, in the context of the family, the school, and the community.

Treatment involves very much more than saying " don't worry ". The parents of a child with symptoms

*should* worry, and should go on worrying until he is better. Reassurance which does not reassure merely wastes time; there should be no reassurance without explanation. The aims of treatment are simply stated, though their application is often complex and they must be varied to suit each patient:

First, the doctor should unearth the fears of some specific complaint (such as tuberculosis) and remove them. The mere verbalisation of fears often abolishes them and the symptom. He may then go on to explain how the symptom can arise without an organic cause, as an exaggeration of normal reactions.

Second, he should encourage the parents and the child to " blow off steam ". The release of emotional tension goes with a sympathetic discussion of topics about which parents and child feel strongly. It is often helpful to talk with the child, or the mother, alone.

Third, he should allay the parents' distress and their feeling that they are blameworthy because their child has a persistent complaint.

Fourth, he should discuss with the parents the road they should take, and give friendly guidance on how the harmful aspects of the child's environment may be modified. A father may be brought to see that he should " loosen the rein "; a mother that she should take pleasure in finally severing the invisible umbilical cord; and a teacher that the carrot is better than the stick.

In psychosomatic disorders diagnosis and treatment are inextricably mixed together. I am constantly re-learning some elementary lessons about them. Treatment begins with the first words spoken at the first diagnostic consultation; and the more time spent on the history, the less time will be needed for treatment. A last remark about treatment is that doctors who treat the symptom tend to give prescriptions, but doctors who treat the patient prefer to offer guidance.

### Epilogue

In our daily practice psychosomatic disorders seem to be becoming much more common, just as hysteria is becoming rarer. Between the two world wars there were doctors, including Cameron and Winnicott in this country and others abroad, who realised the importance of stress and emotional disorders in children; but their importance relative to infectious diseases and malnutrition, for example, was small. Today the vast ocean of physical illness is receding visibly, and the cliffs of mental and psychosomatic disorder loom larger and more threatening. It is not possible to say whether this is due only to a change in perspective; certainly it is difficult to conceive that stress was uncommon in earlier decades of this century, or in earlier centuries with their wars, plagues, and famines. Many factors must be concerned. But now, with the dramatic successes in preventing and treating hitherto lethal diseases, we are no longer content merely to keep our patients alive: we try now to help them to enjoy being alive. We must surely agree that the earlier psychosomatic disorders are diagnosed and treated, the more likely is the patient to grow up to enjoy health, for " The Child is father of the Man ".

It is a pleasure to thank my friend Dr. R. Mac Keith for his contributions, direct and indirect, to this address.

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## COMPLEMENT-FIXING AUTOANTIBODY TO THYROGLOBULIN IN HASHIMOTO'S DISEASE

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SINCE the demonstration by Roitt et al. (1956) of precipitating antibody, reacting apparently with thyroglobulin, in the serum of patients with Hashimoto's disease, considerable interest has developed in the possible role of auto-immunisation in certain diseases of the thyroid gland (Owen 1958, *Lancet* 1958).

There is now strong evidence that the precipitating antibodies demonstrable in the sera of many patients with Hashimoto's disease, and of some patients with other thyroid abnormalities, react with human thyroglobulin. In general, complement is not fixed by this reaction, but a more sensitive test for the antibodies concerned has been provided by the agglutination of red blood-cells treated with tannic acid and coated with human thyroglobulin. The complement-fixation (C.F.) reaction has been used by several groups of workers to demonstrate antibodies to thyroid-tissue antigens, and while the results obtained have been somewhat conflicting (*Lancet* 1957), it is now clear that the sera of nearly all patients with Hashimoto's disease, of many with primary myxœdema, and of many with thyrotoxicosis contain a C.F. autoantibody which reacts with an antigen quite distinct from thyroglobulin, and most readily demonstrable in extracts prepared from the thyroid glands of thyrotoxic individuals. The features of this C.F. reaction were described first by Trotter et al. (1957) and in more detail by Roitt and Doniach (1958) and Anderson, Goudie, and Gray (1959). We refer to this reaction as the thyrotoxic C.F. reaction.

In the present account we show that the sera of a small proportion of patients with Hashimoto's disease contain, in addition to the usual anti-thyroglobulin precipitins and the thyrotoxic C.F. antibody, a complement-fixing antibody which reacts with thyroglobulin, and which gives rise to a second type of C.F. reaction with extracts of thyroid tissue.

### Materials and Methods

The techniques used for C.F. and precipitin reactions and for zonal electrophoresis have already been described in detail (Anderson et al. 1959), and it is necessary here to provide only a brief summary.

For C.F. tests, 0·1 ml. volumes of suitable dilutions of serum, complement (guineapig serum), and antigen (saline extracts of human thyroid or other tissues) were incubated for 1 hour at 37°C, and residual complement was detected by adding 0·5 ml. of a 3% suspension of sheep red cells sensitised with immune horse serum: the degree of lysis was observed after a further hour at 37°C and the results were recorded as: — (complete lysis) to +++ (no lysis). Test sera and thyroid extracts were used only in dilutions having an anticomplementary activity of less than 1 M.H.D. and 0·5 M.H.D. of complement respectively, and 2·5 M.H.D. of complement was used in the tests. Care was taken to perform precise control tests of anti-complementary activity, and by this means it was possible to test low dilutions of serum and thus to detect antibodies present in low titre. Organ extracts other than thyroid were used to test the antibodies for

organ-specificity; and, as these were in some instances rather strongly anti-complementary, dilutions with anticomplementary activity up to 1 M.H.D. were sometimes employed to avoid the necessity for excessive dilution, and 3 M.H.D. of complement was then used in the actual tests. Test sera, complement, and tissue extracts were stored at −15°C. Precipitin tests were performed by a modification of the Oudin tube technique (Goudie et al. 1957) and by the method of Ouchterlony.

*Thyroid Extracts*

As reported elsewhere (Anderson et al. 1959) the majority of extracts prepared from the glands of thyrotoxic patients contain readily demonstrable thyrotoxic C.F. antigen, but some such extracts are relatively poor in this antigen. In the present account the term " thyrotoxic extract " is used only for extracts known to contain the antigen in abundance. Naturally, such extracts also contain thyroglobulin. The term " non-toxic extract " is applied to extracts of normal thyroid tissue obtained post mortem, and also to extracts of surgically excised non-toxic colloid goitres. In the latter extracts, all of which contain an abundance of thyroglobulin, the thyrotoxic antigen is either not detectable or is present in amounts too small to fix complement in a significant degree in the dilutions employed.

*Test Sera*

In an investigation of the thyrotoxic C.F. reaction it was observed that the serum (serum 1) from a patient with Hashimoto's disease had the unusual property of reacting to fix complement, not only with thyrotoxic extracts, but also with non-toxic extracts. Subsequently, eight more Hashimoto sera, out of a total of fifty-three tested, were found to participate in C.F. reactions with both types of extract; all nine sera contained precipitin to thyroglobulin. Four of these sera have been further investigated, and the results are described in the following account. Serum 1 has been investigated more fully than the others, and it is convenient to describe in detail the results with this serum, and to indicate more briefly the results with the other three.

## Results with Serum 1

*Patterns of Reaction*

Table I shows the results of testing serum 1 by the method of block titration, in which each of a series of doubling dilutions of the serum was tested with a series of doubling dilutions of thyroid extract. The upper part of the table shows the results with a thyrotoxic extract, the lower part with a non-toxic extract. It is apparent that serum 1 reacts, in low dilutions, with a wide range of dilutions of both extracts, and at higher dilutions with the thyrotoxic extract only. The constancy of these reaction-patterns of serum 1 was established by performing block titrations with five thyrotoxic and four non-toxic (three normal thyroid and one colloid goitre) extracts. By contrast, the majority of Hashimoto sera react to fix complement only with thyrotoxic extracts, and exhibit the reaction pattern (table II) characteristic of thyrotoxic C.F. antibody (Anderson et al. 1959).

TABLE II—C.F. REACTION PATTERN OF A HASHIMOTO SERUM WITH THYROTOXIC EXTRACT

| Serum dilutions | Dilutions of thyroid extract | | | | | | |
|---|---|---|---|---|---|---|---|
| | 2 | 4 | 8 | 16 | 32 | 64+ | Nil |
| 2 | +++ | +++ | +++ | +++ | ± | − | − |
| 4 | +++ | +++ | +++ | ++ | − | − | − |
| 8 | +++ | +++ | +++ | ++ | − | − | − |
| 16 | +++ | +++ | +++ | ++ | − | − | − |
| 32 | +++ | +++ | +++ | ++ | − | − | − |
| 64 | +++ | +++ | +++ | ++ | − | − | − |
| 128 | ++ | ++ | ++ | + | − | − | − |
| 256 | ± | − | − | − | − | − | − |
| 512+ | − | − | − | − | − | − | − |
| Nil | − | − | − | − | − | − | − |

It seemed probable, from its reaction patterns, that serum 1 contained two C.F. antibodies, one of which was the thyrotoxic C.F. antibody, having a titre of 1 in 128, and the other reacting with both thyrotoxic and non-toxic extracts, and having a titre of 1 in 8. This was confirmed by testing 1 in 2 and 1 in 32 dilutions of serum 1 with a large number of thyroid extracts: the former dilution reacted with all extracts, the latter with thyrotoxic extracts only.

*Nature of the Antigen*

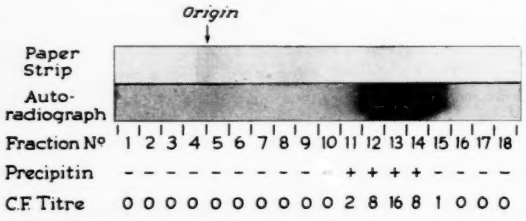
When C.F. titrations were performed upon various thyroid extracts with a 1 in 2 dilution of serum 1, it was found that colloid-goitre extracts had a slightly higher antigenic titre (average 1 in 8000) than thyrotoxic extracts (1 in 2000), and in particular the titres of extracts of the glands of two thyrotoxic patients treated preoperatively with potassium perchlorate were much lower (1 in 64 and 1 in 256); these two glands contained only very small amounts of colloid, and a relationship thus seemed to exist between the amount of colloid present in a gland and its antigenic titre in C.F. reactions with a 1 in 2 dilution of serum 1. This suggested that the antigen concerned was thyroglobulin.

*Reaction with human thyroglobulin.*—C.F. tests with serum 1 and a solution of human thyroglobulin, prepared by the method of Derrien et al. (1948), gave a reaction pattern similar to that with non-toxic extracts (table I), the serum having an antibody titre of 1 in 8 and reacting with dilutions of thyroglobulin solution up to 1 in 1280. Control tests with normal sera, and Hashimoto sera containing only thyrotoxic C.F. antibody and precipitin, were negative.

*Immunoelectrophoresis.* — Tests with electrophoretic fractions of thyroid extracts also suggested that the antigen was thyroglobulin. 0·02 ml. of thyroid extract was subjected to paper-electrophoresis, and a central longitudinal strip was removed from the paper, dried, and stained for protein. The two lateral strips were cut into transverse

TABLE I—C.F. REACTION PATTERNS OF SERUM 1 WITH THYROTOXIC AND NON-TOXIC THYROID EXTRACTS

| Reaction | Serum dilutions | Dilutions of thyroid extract | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | 2 | 4 | 8 | 16 | 32 | 64 | 128 | 256 | 512 | 1000 | 2000 | 4000 | 8000 | 16,000+ | Nil |
| With thyrotoxic extract | 2 | +++ | +++ | +++ | +++ | +++ | +++ | +++ | +++ | +++ | +++ | +++ | + | − | − | − |
| | 4 | +++ | +++ | +++ | +++ | +++ | +++ | +++ | +++ | +++ | +++ | +++ | + | − | − | − |
| | 8 | +++ | +++ | +++ | +++ | ++ | ++ | +++ | +++ | +++ | +++ | ++ | − | − | − | − |
| | 16 | +++ | +++ | +++ | ± | − | − | − | + | + | − | − | − | − | − | − |
| | 32 | +++ | +++ | ++ | − | − | − | − | − | − | − | − | − | − | − | − |
| | 64 | +++ | +++ | ++ | − | − | − | − | − | − | − | − | − | − | − | − |
| | 128 | +++ | +++ | ± | − | − | − | − | − | − | − | − | − | − | − | − |
| | 256+ | − | − | − | − | − | − | − | − | − | − | − | − | − | − | − |
| | Nil | − | − | − | − | − | − | − | − | − | − | − | − | − | − | − |
| With non-toxic extract | 2 | +++ | +++ | +++ | +++ | +++ | +++ | +++ | +++ | +++ | +++ | +++ | +++ | + | − | − |
| | 4 | +++ | +++ | +++ | +++ | +++ | +++ | +++ | +++ | +++ | +++ | +++ | +++ | ± | − | − |
| | 8 | ++ | ++ | ++ | ++ | ++ | ++ | ++ | +++ | +++ | +++ | +++ | ++ | − | − | − |
| | 16 | − | − | − | − | − | − | − | − | + | + | ± | − | − | − | − |
| | 32+ | − | − | − | − | − | − | − | − | − | − | − | − | − | − | − |
| | Nil | − | − | − | − | − | − | − | − | − | − | − | − | − | − | − |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Paper Strip
Auto-radiograph
Fraction No 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18
Precipitin - - - - - - - - - - + + + + - - - -
C.F. Titre 0 0 0 0 0 0 0 0 0 0 2 8 16 8 1 0 0 0

**Immunoelectrophoresis and autoradiography of the electrophoretic strip of a radioactive thyroid extract.**

pieces of 7 mm. width; one set of transverse pieces was placed in the cups of Ouchterlony plates and tested for precipitating antigen (i.e., for thyroglobulin). Each of the other set of transverse pieces of paper was extracted with 0·5 ml. of saline solution and was tested for anti-complementary activity and titrated for C.F. antigen, using a 1 in 4 dilution of serum 1 as antibody. This procedure was performed with four thyroid extracts (two from colloid goitres, one from normal thyroid tissue, and one from a thyrotoxic patient); in all cases the electrophoretic fractions giving C.F. reactions were those containing precipitating antigen. Immunoelectrophoresis was also carried out with an extract of a thyroid gland from a patient who had received radio-iodine shortly before thyroidectomy, and autoradiography of the stained central part of the strip showed the C.F. and precipitating antigens to correspond to the radioactive protein fraction—i.e., to thyroglobulin (see figure).

It is concluded from the above experiments that the C.F. antibody of titre 1 in 8 in serum 1 reacts with thyroglobulin.

*Relationship of Thyroglobulin C.F. Antibody to Precipitin*

Since there is convincing evidence that the precipitating antibody present in the serum of the majority of patients with Hashimoto's disease reacts with thyroglobulin (Doniach and Roitt 1957) the question arises whether the C.F. anti-thyroglobulin present in serum 1 participates in the precipitin reaction. This was investigated by testing specific precipitates for anticomplementary activity, and by " blocking " tests.

*Anticomplementary activity of specific precipitates.*—1 ml. of serum 1 was mixed with 1 ml. of the predetermined dilution of a non-toxic thyroid extract which resulted in the formation of the largest amount of precipitate. After 48 hours at 4°C the mixture was centrifuged, the supernatant was withdrawn, and the precipitate was washed thrice and made up to 1 ml. with saline solution. 0·1 ml. amounts of the suspended precipitate were then incubated with a series of increasing quantities of complement, and after 1 hour at 37°C residual complement was demonstrated in the usual manner. The precipitate was shown to be capable of fixing more than 16 M.H.D. of complement. By contrast, Hashimoto sera which contained precipitins and thyrotoxic C.F. antibody but no detectable thyroglobulin C.F. antibody reacted with non-toxic extracts to yield precipitates which were virtually devoid of C.F. properties.

*Blocking of the C.F. thyroglobulin reaction.*—Although the inhibiting effect of " blocking " antibody is best known in relation to isoagglutination of erythrocytes, it has also been described in C.F. reactions (Zinsser and Parker 1923), and it seemed possible that the failure of most Hashimoto sera to fix complement in their reaction with thyroglobulin might be attributable to the presence of " blocking " antibody. Accordingly, serum 1 was mixed with such a Hashimoto serum, and the mixture was tested for C.F. properties with non-toxic extract. By this means it was shown that most Hashimoto sera are capable of " blocking " the C.F. thyroglobulin reaction; but the effect was always weak, and was observed with only high dilutions of non-toxic extract. It therefore seems unlikely that " blocking " antibody is an important factor in determining whether or not a Hashimoto serum fixes complement in its reaction with non-toxic extract.

**Results with Other Sera**

The results with the four sera investigated are summarised in table III. In all, the reaction patterns in block titrations were similar to those of serum 1. Thyrotoxic C.F. antibody titres were somewhat higher than is usual in Hashimoto's disease, and the C.F. anti-thyroglobulin titres varied up to 1 in 8. The C.F. antigen titre of a non-toxic extract was much lower for sera 3 and 4 than for sera 1 and 2; in view of the observations in the previous section, this may possibly be attributable to a " blocking " effect in sera 3 and 4. All four sera reacted to fix complement with a solution of purified thyroglobulin; the concentration of this solution is unknown, but with each serum its titre was slightly lower than that of the non-toxic extract. Three of the sera showed a slight zoning effect in their reactions with non-toxic extract and with thyroglobulin. This is illustrated for serum 1 in table I, in which the serum is seen to react in slightly higher dilution with 1 in 512 and 1 in 1000 dilutions of the thyroid extract. Finally, the reaction of each serum with non-toxic extract yielded a precipitate with C.F. properties, although there was considerable variation in the amounts of complement fixed. The majority of Hashimoto sera, which do not contain thyroglobulin C.F. antibody, yielded precipitates which fixed less than 1 M.H.D. of complement.

TABLE III—RESULTS OF INVESTIGATIONS ON FOUR HASHIMOTO SERA CONTAINING C.F. ANTI-THYROGLOBULIN

| Serum no. | Titre of thyrotoxic C.F. antibody | Titre of thyro-globulin C.F. antibody | Titre of non-toxic extract | Titre of thyro-globulin solution | Zoning | Anti-complementary activity of precipitates* |
|---|---|---|---|---|---|---|
| 1 | 128 | 8 | 8000 | 1280 | + | 16 |
| 2 | 256 | 8 | 2000 | 640 | + | 7 |
| 3 | 64 | 1 | 256 | 160 | + | 3 |
| 4 | 256 | 2 | 256 | 160 | - | 16 |

* Expressed in number of M.H.D. of complement fixed by the precipitates; the other figures represent reciprocals of titres.

Five other Hashimoto sera were observed to react to fix complement with both thyrotoxic and non-toxic extracts, and in four the reaction patterns were similar to those of serum 1: these sera have not been further investigated.

*C.F. Antibodies to Various Organs in Hashimoto's Disease*

In C.F. tests in which extracts of various organs were used as antigens, the majority of sera from patients with thyroid diseases yielded negative results, the C.F. antibodies present reacting specifically with thyroid extracts. In occasional Hashimoto sera, however, C.F. reactions were obtained with extracts of liver, kidney, and other tissues, and this was the case with serum 2. Such reactions were readily distinguishable, by their lack of organ-specificity, from the reaction with adrenal extracts in occasional cases of Addison's disease (Anderson et al. 1957). In the case of serum 2, " non-specific " reactions were not observed with a second sample of serum collected after the patient had been treated for two years with

thyroxin, although precipitin was still readily demonstrable, and thyroglobulin C.F. antibody was only slightly weaker than before.

## Discussion

It now seems clearly established that two distinct antibodies may be associated with thyroid diseases. One of these reacts with thyroglobulin and is demonstrable by the precipitin reaction and also by the tanned-red-cell agglutination technique. The other antibody reacts with a constituent of thyrotoxic thyroid tissue and has been demonstrated by only the complement-fixation reaction. The present account describes a third type of antibody, which reacts with thyroglobulin to fix complement. Its demonstration helps to explain some of the conflicting results which have been reported in C.F. tests in which normal thyroid tissue has been used as the antigen (*Lancet* 1957).

While fixation of complement usually indicates the occurrence of an antigen-antibody reaction, this is not invariably so; and it is desirable to demonstrate that the C.F. properties of the test serum reside in the $\gamma$- or $\beta$-globulin. In the case of C.F. antibodies of low titre this is difficult to achieve, and it has not been done in the present investigation. Nevertheless, the general features of the thyroglobulin C.F. reaction, and in particular its specificity, point strongly to its immunological nature. The immunoelectrophoretic experiments described, and the demonstration of the reaction with a chemically purified solution of thyroglobulin, provide strong evidence that the antigen concerned is thyroglobulin.

The demonstration that the C.F. antibody participates in the formation of specific precipitates, and may be blocked by sera containing precipitating antibody, is of particular interest, for the immunological nature of the precipitin reaction is not in doubt; the antigen concerned has been shown to be thyroglobulin (Roitt et al. 1958); and we have shown, in unpublished observations, that the precipitins behave as autoantibodies, reacting with the patients' own thyroid extracts. We therefore feel justified in concluding that the C.F. reaction described is of an immunological nature, that the antigen is thyroglobulin, and that the antibody may justifiably be termed an autoantibody. This last conclusion could not be confirmed directly; for thyroid tissue was not available from any of the four patients providing the sera, and in any case we have found extracts of Hashimoto thyroid glands to be too highly anticomplementary to be used in C.F. tests.

White (1957) reported a C.F. reaction between a Hashimoto serum and a solution of thyroglobulin prepared by the method of Derrien et al. (1948), but the reaction pattern was quite different from that observed by us. Roitt and Doniach (1958) observed little or no complement-fixation in the reactions of Hashimoto sera with thyroglobulin, probably because the techniques they used for C.F. reactions were not suited to the demonstration of low-titre antibodies. Although the C.F. antibodies to thyroglobulin were of low titre, they nevertheless reacted with high dilutions of thyroid extracts and of thyroglobulin solution, and we have found them to be of value in detecting thyroglobulin in lower concentrations than can be demonstrated by the precipitin reaction.

One of the most interesting problems in Hashimoto's disease concerns the cause of the destructive process in the gland. Although it seems probable, by analogy with the experimental auto-immune thyroiditis produced in animals (Witebsky and Rose 1956, Witebsky et al. 1957), that auto-immunisation plays a pathogenic role in Hashimoto's disease, it remains undecided which, if any, of the autoantibodies demonstrated is the cytotoxic one. Roitt et al. (1958) and Roitt and Doniach (1958) have advanced objections to the precipitin being the agent responsible, and have pointed out that the presence of complement is obligatory to the destructive action of certain cytotoxic antibodies. Despite its low incidence and titre, the unlikely possibility that C.F. antibody to thyroglobulin is of pathogenic importance cannot be excluded with certainty; for the rate of its production, and of its absorption by the thyroid tissue, remain unknown.

The demonstration that the sera of occasional patients with thyroid diseases react to fix complement, not only with extracts of thyroid tissue, but also with extracts of other organs, has been reported by Roitt and Doniach (1958). We agree with these workers in believing that the thyroid antibodies are organ-specific and are not responsible for the additional reactions. In our experience the " non-specific " reactions have been encountered especially in Hashimoto's disease; and if, as seems likely, they are of an immunological nature, then they probably represent another feature consequent on the abnormal immunological status of individuals with this condition.

## Summary

Complement-fixation reactions were performed on the sera of patients with Hashimoto's disease, using as antigen extracts of normal human thyroid tissue and of colloid goitres. Positive reactions were observed with nine of fifty-three sera tested. Investigations on four of the positive sera are described, and it is concluded that the reaction is of an auto-immunological nature, and that the antigen concerned is thyroglobulin.

The complement-fixing antibodies to thyroglobulin were present in low titres, but nevertheless are useful and sensitive reagents for the immunological detection of thyroglobulin. They were shown to participate in the formation of specific precipitates, and under certain conditions their reaction with thyroglobulin was blocked by the precipitin present in most Hashimoto sera.

These findings help to explain the conflicting results reported in complement-fixation reactions in which normal thyroid tissue was used as the antigen. It is unlikely that the antibodies described play an important part in the pathogenesis of Hashimoto's disease.

We wish to thank the physicians and surgeons who have willingly cooperated in providing specimens of blood and surgical material. The solution of purified thyroglobulin was kindly supplied by Dr. A. E. Stuart and Dr. W. S. A. Allan, of the University Department of Pathology, Edinburgh. This investigation was assisted by a financial grant to one of us (J. R. A.) by the Department of Health for Scotland.

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# INVESTIGATIONS OF THYROID ANTIGENS REACTING WITH HASHIMOTO SERA

## EVIDENCE FOR AN ANTIGEN OTHER THAN THYROGLOBULIN

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THE occurrence of anti-thyroid antibodies in the sera of patients with Hashimoto's thyroiditis was first described by Roitt, Doniach, Campbell, and Hudson (1956), and more detailed accounts have been given by Doniach and Roitt (1957), Roitt, Campbell, and Doniach (1958), and Roitt and Doniach (1958). These antibodies were first detected by precipitation techniques and were shown to be directed against the thyroglobulin fraction of thyroid extracts. The use of the complement-fixation reaction has suggested that antibodies against other distinct components of the thyroid gland may be present in the sera of some cases (Trotter et al. 1957). In this paper we present further evidence of the existence of antibodies corresponding to a "specific" thyroid antigen distinct from thyroglobulin.

### Materials and Methods

*Thyroid antigens* were prepared by three methods:

*Crude mince.*—In the earlier stages of the work antigens were prepared by chopping about 1 g. (wet weight) of thyroid with a scalpel and suspending in 5 ml. of unbuffered physiological saline. After overnight standing at +4°C the suspended tissue was centrifuged at 2000 r.p.m. for ten minutes. The supernatant fluid constituted the antigen preparation.

*Homogenates* of thyroid gland were prepared in a Waring-type blender or an all-glass homogeniser. About 1 g. (wet weight) of thyroid was homogenised per 5 ml. of physiological saline with or without the addition of 0·05*M* borate or phosphate buffer, pH 7·6. The suspension was usually clarified by immediate centrifugation in the cold at 2000 r.p.m. for ten minutes. The nature of the suspending medium did not appear to influence the efficiency of antigenic extraction. This technique was introduced at a later stage and was used in the majority of the experiments reported here.

*Extracted homogenates.*—In some instances homogenisation was preceded by an extraction stage in order to remove as much of the thyroglobulin as possible. Frozen thyroid gland was sliced as thinly as possible by hand and the slices laid on frozen borate-buffered saline. This was allowed to thaw at +4°C without further disturbances. The solution was removed after standing overnight and the slices homogenised as described above.

All these thyroid extracts were stored frozen at −10°C and appeared to retain their complement-fixing potency for up to eighteen months.

*Thyroglobulin.*—Semipurified thyroglobulin was prepared by differential ammonium-sulphate precipitation by the method of Derrien et al. (1948), as applied to human thyroids by Roche et al. (1952).

*Sera.*—Only human sera were used. These were obtained from cases of thyroid disease and after inactivation at 56°C for thirty minutes were stored frozen at −10°C.

*Complement-fixation* (C.F.).—The "chessboard" micromethod described by Belyavin (1953) was used throughout. C.F. potencies were expressed as the total number of antigen-antibody mixtures giving detectable fixation. Fresh guineapig serum complement and "stabilised" complement (Richardson 1941) as supplied by Burroughs Wellcome & Co. were used indifferently.

*Flocculation reactions.*—Antisera were absorbed with semipurified thyroglobulin by precipitation at 40°C in the equivalence zone. Optimal proportions were determined by quantitative flocculation in tubes at 40°C by the *a* procedure of Dean and Webb (1926).

*Agar-gel precipitations* were performed by the method of Doniach and Roitt (1957). The agar contained 1% sodium azide and the incubation was at room temperature.

*Nitrogen content* was determined by a micro-Kjeldahl method.

### Results

#### COMPLEMENT-FIXATION WITH SERA FROM CASES OF THYROID DISEASE

*Source of Complement-fixing Antigen*

Early in this investigation it became apparent that the type of tissue used as source of antigen for the complement-fixation test was critical.

Initially crude minces and homogenates of normal thyroid gland, obtained either post mortem or operatively were used and gave uniformly negative results with a number of sera from cases of Hashimoto's disease. On the other hand, homogenates of thyrotoxic glands, removed at operation, proved very active, and gave positive fixation with Hashimoto antisera, even in the absence of a detectable gel-precipitation reaction. This was in contradistinction to the gel-precipitation results, which showed that reactive sera would give precipitation with antigen derived from either normal or thyrotoxic glands. Extracts of simple goitres also failed to give positive fixation, and it was therefore obvious that thyrotoxic glands were particularly rich in some antigenic component, possibly distinct from the precipitating antigen.

TABLE I—C.F. REACTIVITY OF THYROID-GLAND PREPARATIONS

| Hashimoto sera (non-precipit.) | Type of gland | | | |
|---|---|---|---|---|
| | Normal | Simple goitre | Toxic diffuse goitre | Hashimoto |
| Case A: sample B2 .. | 0/5 | 0/1 | 6/6 | 0/1 |
| sample B3 .. | 0/2 | 0/1 | 8/12 | .. |

Numerator = no. of preparations giving fixation.
Denominator = total no. tested.

Homogenates of thyrotoxic gland were adopted as the standard type of antigen for the complement-fixation test.

A summary of the complement-fixing reactivity of various types of thyroid-gland extract, tested against two successive serum samples (precipitation-negative) from a case of Hashimoto's disease are given in table I.

*Complement-fixation and Precipitation*

Using homogenates of thyrotoxic thyroid it was readily shown that several sera from cases of Hashimoto's disease contained complement-fixing antibodies, although apparently negative in the gel-precipitation test. It was not clear at first whether this was a reflection of the relative sensitivities of the two tests, or whether distinct antigen-antibody systems were involved.

206 sera from cases of thyroid disease, and 36 sera from a variety of non-thyroid conditions, were tested by complement fixation, many of these sera having previously been examined by the gel-precipitation method. (In all except a few, for which histological evidence was available,

TABLE II—COMPLEMENT-FIXATION AND GEL-PRECIPITATION REACTIONS IN SERA FROM CASES OF THYROID DISEASE

| Sera | | C.F. test | | Gel-ppn | |
|---|---|---|---|---|---|
| Source | No. tested | + | − | + | − |
| Hashimoto .. .. | 64 | 51 | 13 | 27 | 37 |
| Myxœdema .. .. | 19 | 10 | 9 | 4 | 15 |
| Thyrotoxicosis .. | 66 | 28 | 38 | 6 | 60 |
| Simple goitre .. .. | 33 | 4 | 29 | 0 | 33 |
| Carcinoma of thyroid .. | 25 | 6 | 19 | 6 | 19 |
| No thyroid disease .. | 36 | 2 | 34 | 0 | 36 |
| Totals .. .. | 243 | 101 | 142 | 43 | 200 |

TABLE III—SERA GROUPED ACCORDING TO GEL-PRECIPITATION AND LEVEL OF COMPLEMENT-FIXING POTENCY

| Serological class | C.F. potency: 1–8 | C.F. potency: >8 |
|---|---|---|
| Gel-ppn, positive .. | 9 | 6 |
| Gel-ppn, negative .. | 12 | 11 |
| Proportion of ppns positive | 9/21 | 6/17 |

the diagnoses were purely clinical.) Table II shows that of the sera obtained from cases of Hashimoto's disease, myxœdema, and thyrotoxicosis a considerable proportion gave a positive complement-fixation test and a negative gel-precipitation.

Although many of the precipitation tests were carried out with normal thyroid extracts, there is no reason to believe, from the results obtained with both types of antigen, that these results would have been any different had all the precipitations been performed against a thyrotoxic-gland antigen. Thus if the discrepancy was due to the complement-fixation reaction being the more sensitive test for antibody, the occurrence of an appreciable number of precipitation-positive and C.F.-negative sera would be unlikely. In this series, such sera formed about 4% of the total. Moreover, if all the sera were to be classed according to their C.F. potency, more precipitation-positive sera should occur in the groups with highest C.F. potencies. This, in fact, was not the case (table III).

TABLE IV—COMPARISON OF COMPLEMENT-FIXING POTENCY AND THYROGLOBULIN CONTENT OF NORMAL-GLAND AND THYROTOXIC-GLAND EXTRACTS

| Thyroid extract | Complement-fixation against | | | | Mg. standard thyroglobulin per ml. | Mg. N per ml. |
|---|---|---|---|---|---|---|
| | Serum: Yg | | Serum: Pr | | | |
| | Potency | % activity | Potency | % activity | | |
| Normal 1 | 14 | 11 | 8 | 12·5 | 1·57 | 0·30 |
| Normal 2 | 15 | 11·5 | 4 | 6·0 | 2·7 | 0·39 |
| Thyrotoxic 1 | 43* | 100 | 24 | 100 | 2·7 | 0·59 |
| Thyrotoxic 2 | 42 | 94 | 19 | 50 | <1·0 | 0·19 |

* The C.F. potency of this extract has been arbitrarily taken as 100%. The % activity of the other extracts has been calculated relative to this.

On these grounds, the possibility of at least two antibodies reacting with distinct antigenic components was considered.

## EVIDENCE FOR THE PRESENCE OF TWO DISTINCT ANTIGENIC COMPONENTS IN THYROID GLAND

### *Thyroglobulin Content and C.F. potency*

It had been previously shown (Roitt, Campbell, and Doniach 1958) that the precipitating antibodies in the sera of Hashimoto cases were principally directed against thyroglobulin. A comparison was therefore made between the complement-fixing potency and the thyroglobulin content of extracts of normal and tyrotoxic gland.

The complement-fixation assays were carried out against two Hashimoto sera in parallel, both of them precipitin-negative. The thyroglobulin content was estimated by optimal-proportions precipitations, using the *a* procedure (Dean and Webb 1926) with a human serum which had previously been standardised for thyroglobulin-flocculating potency against a semipurified preparation of human thyroglobulin. The results could therefore be expressed in milligrammes of "standard" thyroglobulin preparation per ml. Two normal-gland homogenates were compared in this way against two thyrotoxic-gland preparations identically prepared.

From table IV it is obvious that the thyroglobulin concentration in thyroid-gland extracts varies independently of the complement-fixing potency, and the much greater C.F. activity of the thyrotoxic homogenates is confirmed.

### *Varying Complement-fixation "Pattern" with Crude Gland Extracts and Thyroglobulin*

Hashimoto sera were found which gave complement-fixation with semipurified thyroglobulin as antigen, although they did not flocculate with thyroglobulin in tube tests. It could be argued that the observed C.F. reaction was due to adventitious antigenic contamination. This question was partially clarified by the shape of the

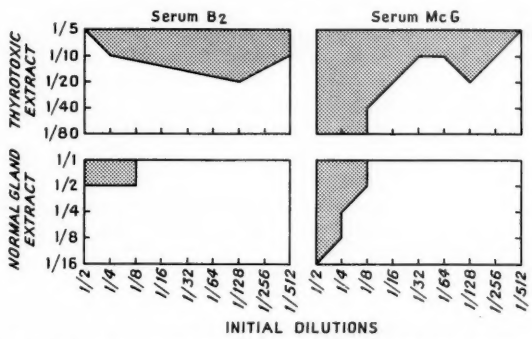


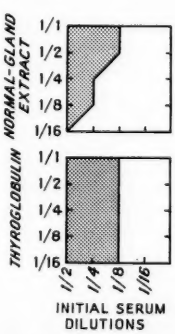

**Fig. 1—Complement-fixation patterns obtained with two human Hashimoto sera when tested against normal and thyrotoxic thyroid-gland extracts.**

"fixation area" obtained with different antigens in "chessboard" tests.

The "fixation area" observed with normal-gland homogenate was characteristically as illustrated in fig. 1, serum McG. As can be seen, however, the same serum, when tested against whole thyrotoxic-gland extract, gave a pattern of a different nature. When the same antigens were tested against the Hashimoto serum B2 (fig. 1), very little reaction could be detected against the normal-gland antigen, and against thyrotoxic homogenate a fixation area of markedly different shape was obtained. This particular serum did not give a precipitation reaction with either thyroglobulin or whole-gland homogenate, and could be assumed to contain no detectable anti-thyroglobulin antibody.

On this basis, the fixation pattern given by this serum with thyrotoxic gland must be due to antibody other than anti-thyroglobulin antibody, and consequently serum McG. must be regarded as containing both antibodies, thus yielding a complex pattern against the thyrotoxic-gland homogenate.

A comparison of the fixation area given by serum McG. against semipurified thyroglobulin with that obtained with normal-gland homogenate (fig. 2) indicated that the latter reaction must be due to the thyroglobulin in the extract. This deduction was entirely consistent with the assumptions already made with regard to the antibody content of the sera B2 and McG.




To summarise, it was concluded that where a serum contained C.F. antibodies against thyroglobulin only, a characteristic "area of fixation", lengthened predominantly towards the higher antigen dilutions, would result. C.F. antibodies of the other kind would be expected to yield an area lengthened markedly towards the higher serum dilutions. Where the two antibodies occurred

**Fig. 2—Complement-fixation patterns shown by normal thyroid-gland extracts, and normal-gland thyroglobulin when tested against a Hashimoto serum (McG).**

simultaneously a superimposed pattern of the kind shown by serum McG. against thyrotoxic homogenate would be found. From these conclusions, it was decided that an inspection of the fixation area would indicate the probable antibody composition of a given serum; explicit in these decisions was the recognition that in fact two distinct antibodies were detectable in these human sera. Corresponding to these antibodies there had to be two antigens in thyroid-gland homogenates, of which one appeared to be thyroglobulin. The other component characterised by the pattern given by serum B2 (fig. 1) with thyrotoxic gland was provisionally termed " thyrotoxic C.F. factor " (T.C.F. factor). For convenience the fixation-area patterns corresponding to these components will be referred to respectively as the " antigen-sensitive " and " antibody-sensitive ".

*Serum Absorption Experiments*

To confirm directly the antigenic non-identity of T.C.F. factor and thyroglobulin, selected human sera were absorbed with semipurified thyroglobulin, using the data obtained from the tube flocculation tests.

For this purpose, equal volumes of thyroglobulin dissolved in physiological saline and undiluted (or diluted 1/5) serum were mixed so as to give an optimally reacting mixture, within the equivalence zone of the system. The mixture was placed in the water-bath at 40° C, and allowed to remain until visual flocculation was complete. The tubes were then removed and held at +4 C overnight. The resulting precipitate was sedimented and packed by low-speed centrifugation, and the supernatant was drawn off, as the absorbed serum. In each case the same serum identically diluted by mixing with simple diluent was put through the same procedure in parallel, thus giving an equivalent unabsorbed control.

TABLE V—EFFECT OF ABSORBING SERA WITH THYROGLOBULIN ON COMPLEMENT-FIXATION AND PRECIPITATION REACTIONS

| Serum | Tested against | Method | Result | |
|---|---|---|---|---|
| | | | Unabsorbed | Absorbed with thyroglobulin |
| Nn | Thyroid extract | C.F.T. | 12 | 12 |
| | Thyroglobulin | C.F.T. | 12 | 0 |
| | | gel-ppn | Positive | Negative |
| Ce | Thyroid extract | C.F.T. | 12 | 14 |
| | Thyroglobulin | C.F.T. | 0 | 0 |
| | | gel-ppn | Positive | Negative |

The absorbed and unabsorbed sera in each case were tested for residual anti-thyroglobulin antibody, by the gel-precipitation method and in addition by complement-fixation in those cases where the serum initially gave positive fixation with thyroglobulin. In parallel, initial and residual antibody against T.C.F. factor was measured by complement-fixation, using a suitable thyroid extract.

These absorption results are illustrated in table V. It should be noted that reciprocal absorptions with T.C.F. factor have not, so far, been carried out. Evidence of complete absorption of thyroglobulin antibody was obtained with both sera. Similar results have been obtained with other sera and other thyroglobulin preparations.

It is evident that complete removal of antibody against thyroglobulin did not affect the complement-fixing potency of the serum against T.C.F. factor. Even in the absence of reciprocal absorption tests, this seems to be clear evidence of the serological dissimilarity of these two substances. It is worth noting that these absorptions removed both flocculating and complement-fixing activity against thyroglobulin. Therefore, with this antigen, both complement-fixation and flocculation are probably mediated by a specific antibody.

TABLE VI—COMPLEMENT-FIXING POTENCY OF FLUID USED FOR WASHING THYROID SLICES COMPARED WITH HOMOGENATE OF THE WASHED SLICES

| Thyroid | Overnight washings | | | | Gland homogenate | | | |
|---|---|---|---|---|---|---|---|---|
| | G. wet wt. of gland per ml. | Mg. N per ml. | Estimated thyroglobulin content (mg. per ml.) | C.F. factor | G. wet wt. of gland per ml. | Mg. N per ml. | Estimated thyroglobulin content (mg. per ml.) | C.F. factor |
| B | 0·1 | 1·01 | 4·5 | 2 (20%) | 0·2 | 0·96 | 4·5 | 9 (100%) |
| D | 0·05 | 0·88 | .. | 5 (60%) | 0·05 | 0·99 | .. | 8 (100%) |
| E | 0·05 | 0·48 | 4·5 | 3 (6%) | 0·2 | 0·61 | 4·5 | 29 (100%) |
| F | 0·05 | 1·30 | 2·2 | 12 (14%) | 0·2 | 1·01 | <1·1 | 29 (100%) |

PROBABLE NATURE AND DISTRIBUTION OF T.C.F FACTOR

*Ease of Extraction of the Two Antigens*

Several toxic goitres were carefully sliced by hand in the frozen state as described in the preparation of extracted homogenates. The extracting buffer was tested for C.F. potency against specific T.C.F. factor serum after overnight contact with the slices at +4° C. At the end of each experiment the slices were homogenised and also tested in the same way. It is evident from the data thus obtained (table VI) that less T.C.F. factor could be extracted into the buffer in this way than could be recovered by total homogenisation of the gland slices. On the other hand, thyroglobulin could be readily demonstrated in as high a concentration in the extracting buffer as in the final homogenate, and this was paralleled by the corresponding nitrogen values. It appears that by simple contact of the gland material with a buffer solution thyroglobulin can be extracted more readily than T.C.F. factor, and this suggests, at least, a different location of these two components in the substance of the thyroid.

*High-speed Centrifugation*

In view of these results it seemed likely that the T.C.F factor has a larger particle than thyroglobulin, and that these two entities would be separable by differential centrifugation. A series of thyroid-gland extracts in buffered saline were subjected to centrifugation at various relative centrifugal force (R.C.F.) values. Table VII gives a representative selection of the results. These indicate that a critical R.C.F. value could be deduced, above which nearly complete sedimentation of specific complement-fixing activity would result. However, such results could not be regularly repeated. Thus it can be seen

TABLE VII—COMPLEMENT-FIXING POTENCY OF SUPERNATANT AND DEPOSIT AFTER CENTRIFUGATION OF THYROID EXTRACTS AT VARYING R.C.F. VALUES

| Expt. | Gland extract | R.C.F. (×g) | Time (min.) | Concentration factor | C.F. potency of fractions | | |
|---|---|---|---|---|---|---|---|
| | | | | | Initial | S.N.F. | Resuspended deposit |
| 1 | A | 7400 | 60 | ×1 | 11 (100%) | 10 (76%) | 3 (10%) |
| 2 | B | 11,700 | 60 | ×1 | 20 ,, | 10 (17·5%) | 14 (35%) |
| 3 | B | 16,750 | 60 | ×1 | >22 ,, | 8 (<10%) | 12 (~19%) |
| 4 | C | 18,200 | 60 | ×2 | 10 ,, | 0 (0%) | 15 (110%) |
| 5 | C | 18,200 | 60 | ×2 | 14 ,, | 0 ,, | 17 (71%) |
| 6 | D | 19,600 | 60 | ×2 | 23 ,, | 0 ,, | 11 (30%) |
| 7 | E | 60,000 | 60 | ×1 | 29 ,, | 0 ,, | 31 (119%) |
| 8 | F | 60,000 | 60 | ×1 | 29 ,, | 5 (7%) | 21 (40%) |

S.N.F.=supernatant fluid.

from the table that at least in one instance centrifugation at the highest R.C.F. value (60,000×*g*) did not achieve total sedimentation. Systematic investigation has shown that certainly with some thyroid extracts the ease with which the T.C.F. factor can be sedimented may be a function of the time and possibly the conditions of storage.

To obtain some indication of the probable size range of T.C.F. factor, or of the particles associated with it, differential centrifugation by the method of Schneider (1948) was carried out.

This entailed centrifuging at increasing speed in the presence of isotonic concentration of sucrose, and estimating the specific complement-fixing activity of the supernatant fluids and deposits at each stage. (The detailed scheme of speeds is indicated in fig. 3.) A separate experiment indicated that the C.F. test was not impaired by the presence of the sucrose, and therefore the various fractions could be tested without further treatment. The bulk of the C.F. activity in this case was recovered in the deposit from the penultimate centrifugation in what Schneider considered to be the microsomal fraction. It is, however, obvious that the active material may only be attached to a complex of large size, and occasional dissociation may occur under conditions which cannot be defined with certainty at this stage. Such a possibility could account, in our view, for the occasionally anomalous behaviour of the T.C.F. factor under differential centrifugation.

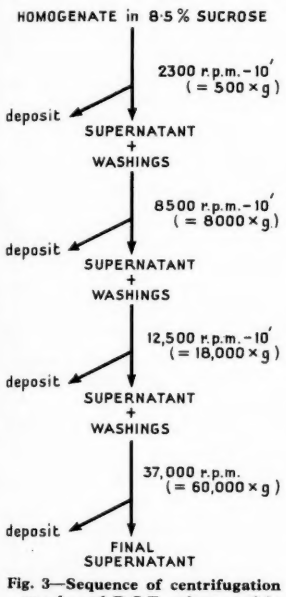



**Fig. 3—Sequence of centrifugation speeds and R.C.F. values used in sucrose gradient analysis of crude thyroid gland extract.**

The pattern of complement-fixation obtained in the deposit and supernatants from centrifugation experiments indicated that a separation had been achieved between T.C.F. factor and thyroglobulin (fig. 4). The sera used in these experiments were amongst the small number that gave complement-fixation against both semipurified thyroglobulin and T.C.F. factor. The pattern of the supernatants is of the antigen-sensitive type previously associated with thyroglobulin, whereas that of the deposits is of the antibody-sensitive kind.

*Experiments with Labelled Iodine*

To study in more detail the distribution of thyroglobulin after differential centrifugation of extracts, thyroids were used from patients who had been previously given tracer doses of $^{131}I$. In addition this would indicate whether the C.F. factor itself was an iodine-carrying compound.

Patients with thyrotoxicosis were selected, because it was expected that their glands would be rich in C.F. factor. The use of this type of patient, however, meant that the $^{131}I$ had to be given at a time when they were receiving anti-thyroid drugs and iodine. Although the $^{131}I$ was given forty-eight hours before operation, the effect of these drugs resulted in the bulk of the iodine being in the form of iodide at the time of removal of the thyroid. All $^{131}I$ estimations, therefore, had to be referred to the fractions precipitable with 50% ammonium sulphate, because it has been shown that human thyroglobulin is completely precipitated at this concentration (Roche et al. 1952).

Immediately after removal the thyroid was homogenised in buffered saline (pH 7·6) to give an approximate 20% wet weight suspension, and clarified by centrifugation at 2000–4000 r.p.m./10 in. The supernatant fluid, which was designated as the starting material, was then centrifuged at between 16,000 and 20,000×*g*. The deposit was washed once with buffered saline, and resuspended finally in a suitable volume of the same. An equal volume of saturated ammonium sulphate was then added to similar aliquots of the starting material, the supernatant fluid, and the resuspended deposit. These mixtures were left at room temperature overnight. The precipitates were separated by centrifugation and dissolved in 3 ml. of 10% sodium hydroxide, and these solutions were then counted in parallel in a well-type scintillation counter. Simultaneously, the unprecipitated supernatant fluid was put up against a human anti-thyroglobulin serum, and the specific antigen-antibody precipitate obtained at equivalence collected by centrifugation. This served to give an estimate of the total thyroglobulin content of the supernatant; and the $^{131}I$ count, estimated in parallel with the other fractions, gave a check on the specificity of the serum reaction and on the efficiency of the ammonium-sulphate precipitation of the thyroglobulin.

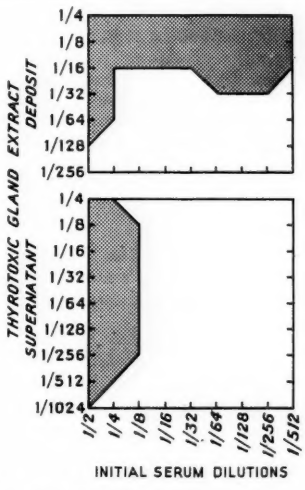



**Fig. 4—Separation of the two complement-fixation patterns from the same sample of thyrotoxic-gland extract (serum McG) by high-speed centrifugation.**

Of four thyrotoxic glands, the first three were treated as described above. In the fourth case certain modifications were introduced. Thus initially the gland was frozen, sliced and extracted as previously described under Materials and Methods. Subsequent centrifugation of the homogenate in order to sediment the T.C.F. factor was carried out at 60,000×*g*. All other manipulations were as already described.

TABLE VIII—PARTITIONING OF C.F. FACTOR AND THYROGLOBULIN BY CENTRIFUGATION USING $^{131}I$ AS A MARKER

| Gland | Preparation | % C.F. potency against T.C.F. factor | % of total precipitable $^{131}I$ | % $N_2$ | % precipitable $^{131}I$ in specific thyroglobulin floccules |
|---|---|---|---|---|---|
| Bk | Whole extract .. | 100 | 100 | 100 | .. |
| | Centrifuge deposit (60,000×*g*) | 100 | 5 | 24 | .. |
| | Supernatant .. | 0 | 96 | .. | .. |
| Cs | Whole extract .. | 100 | 100 | 100 | .. |
| | Centrifuge deposit (19,600×*g*) | 39 | 2 | 2 | .. |
| | Supernatant .. | 5 | 100+ | 93 | 89·0 |
| EJn | Whole extract .. | 100 | 100 | 100 | .. |
| | Centrifuge deposit (11,700×*g*) | 25 | 1 | 5 | .. |
| | Supernatant .. | 10 | 98 | 97 | 100·0 |
| MJn | Whole extract .. | 100 | 100 | 100 | .. |
| | Centrifuge deposit (19,600×*g*) | 32 | 3 | 7 | .. |
| | Supernatant .. | 4 | 101 | 98 | 110·0 |

Table VIII shows the results. It is evident that the $^{131}I$ precipitated from the supernatant fluids by 50% saturation with ammonium sulphate is almost entirely contained in the thyroglobulin fraction, since it is also completely recovered in the specific precipitate after reaction with an anti-thyroglobulin serum. Similarly, only a very small fraction of the total $^{131}I$ activity precipitated from the starting material with ammonium sulphate is found in the centrifuge deposit. The complement-fixing potencies, however, partition themselves in the reverse sense, in that the greater proportion of the activity appears in the deposit.

It seems reasonable to conclude that the T.C.F. factor is not predominantly an iodine-carrying substance, and that it is physically separable from thyroglobulin by high-speed sedimentation.

*Localisation of T.C.F. factor to the Thyroid*

Up to the present time, we have only limited data with respect to the possible distribution of T.C.F. factor in other tissues of the body. Two antisera which were mono-specific for T.C.F.-factor antibody have been absorbed with human red cells of groups A, B, AB, and O, without any reduction in antibody. Furthermore, two of the patients whose thyroids were found to contain T.C.F. factor had antibodies against it in their serum. It seems very unlikely, therefore, that T.C.F. factor is an antigen belonging to the ABO system.

In one patient with Hashimoto's disease the level of antibody against T.C.F. factor was followed for nineteen months after thyroidectomy, and showed a steady fall over this period, indicating that the thyroid was probably the main reservoir of this antigen. Extracts of thyroid, liver, spleen, kidney, adrenal, lungs, and skin, derived from a fresh cadaver, showed no detectable amounts of T.C.F. factor when tested against a standard antiserum in parallel with an active thyrotoxic extract. Weak activity, however, was detected in an extract of submaxillary gland, and clearly this type of experiment must be repeated in order to confirm the apparent localisation of T.C.F. factor in large quantity to pathological thyroids.

## Discussion

There can now be very little doubt that T.C.F. factor and thyroglobulin are distinct antigens.

Recovery of T.C.F. factor mainly in Schneider's " microsomal fraction " suggests that this substance is probably intracellular, as has already been suggested by Roitt and Doniach (1958). This is further supported by the difficulty of extracting T.C.F. factor without prior tissue homogenisation. If the localisation of T.C.F. factor within the cells of the thyroid could be confirmed, it would support the concept that the pathological changes of Hashimoto's disease are the result of direct antibody action, since the tissues are more likely to be damaged by an intracellular antigen-antibody reaction than by a similar reaction in the interior of the acini.

At present views on the nature of the T.C.F. factor must be purely speculative. It may be either a metabolic derivative of the gland or an entirely extraneous substance. The argument for the second possibility rests on the generally held opinion that the body does not readily make antibodies against its own constituents. To explain the nature of T.C.F. factor on these lines would necessitate regarding it as an infectious agent, possibly a virus. The " virus ", however, would have to be present in many normal glands. Though this explanation is not beyond the bounds of possibility, there is no evidence for it.

Reverting to the first possibility, if T.C.F. factor is a metabolic derivative of the thyroid gland it can be regarded either as participating in the general biochemical activity of the gland, or as a step in the specific pathway of thyroglobulin synthesis. The serological evidence, together with the results of the radioiodine incorporation experiments, indicates, however, that if T.C.F. factor is an intermediate step in thyroglobulin synthesis, it must represent a very early stage in the process. It seems to us much more probable that this substance bears no chemical or metabolic relation to thyroglobulin at all.

The fact that T.C.F. factor occurs in much greater quantity in thyrotoxic glands cannot yet be explained. It is tempting to regard this as the accumulation of an abnormal metabolic product in a pathologically changed gland. This accumulation, however, is not necessarily the result of a pathologically deranged metabolism and may be simply the consequence of the anti-thyroid therapy given to all the patients before the removal of the gland. Clearly the essential point is the true chemical nature of the T.C.F. factor, whose determination must be the next step in the solution of these problems.

## Summary

1. The sera of patients with thyroid disease were examined for precipitating and complement-fixing activity against thyroid extracts. The lack of correlation of these reactions, and their dissociation by specific absorption of sera, indicates that they are mediated by distinct antibodies.

2. Two types of complement-fixation pattern have been encountered. One type is " antibody-sensitive " and is best seen when sera from cases of Hashimoto's disease are tested against extracts of toxic diffuse goitre. The other is " antigen-sensitive " and is found only in some Hashimoto sera; the antigen involved in this reaction appears to be thyroglobulin itself.

3. The antibody-sensitive type of reaction is unaffected by absorption of anti-thyroglobulin antibody.

4. The antigen concerned in the antibody-sensitive type of reaction can be sedimented by centrifugation and appears in the " microsomal " fraction. Centrifuged deposits with high complement-fixation activity contained no detectable thyroglobulin and very little iodine.

We are grateful to Dr. J. R. Anderson for a particularly useful Hashimoto serum, and to Dr. I. M. Roitt and Dr. D. Doniach for sera and a preparation of thyroglobulin. Miss A. Waddams took part in the earlier part of this work, and we also wish to thank Miss F. Spreadbury for her help.

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". . . For all the wonders that science can bring, none can approach the richness and promise of man himself. Why should we, out of selfishness and lack of imagination, lament his birth and try vainly to hinder his begetting, rather than make the world a good place for him to live in ?"—J. D. BERNAL, *New Statesman,* March 14, 1959, p. 368.

# SUBACUTE PULMONARY HYPERTENSION DUE TO CHORIONEPITHELIOMA

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THE mechanisms by which right ventricular stress may be produced by carcinomatous metastases in the lungs were reviewed by Greenspan (1933) and by Storstein (1951). To the resulting condition the term subacute pulmonary hypertension was applied by Brill and Robertson (1937), who regarded it as a distinct clinical entity. Three forms have been described:

(1) Carcinomatous lymphangitis in which the lymphatics are extensively invaded by cancer cells causing compression of alveoli and capillaries without invasion of the blood-vessels.

(2) Carcinomatous lymphangitis in which cancer cells from the perivascular lymphatics compress and invade the small arteries and arterioles producing a pulmonary endarteritis which may be followed by intravascular thrombosis.

(3) A pure embolic form in which the pulmonary arteries and arterioles are occluded by cancer-cell emboli and secondary thrombosis.

Harold (1952) reviewed 154 cases of carcinomatous lymphangitis, and added 24 new cases seen at the Brompton and St. Bartholomew's Hospitals in a period of 4 years. The purely embolic form, however, is sparsely recorded, and in the literature reviewed here only 3 cases were described in detail.

Schmidt (1897) reported the case of a man of 37 who died from a gastric carcinoma and whose lungs at necropsy showed widespread occlusion of the smaller pulmonary arteries by carcinoma cells and vascular thrombi. A similar example was reported by Kutsch (1920), while Mason (1940) had a case associated with carcinoma of the breast. At the time of death there was evidence of right ventricular failure in all of them.

A further example associated with chorionepithelioma was mentioned by McMichael (1948) in a review of pulmonary heart-disease, and we shall describe this case here together with two others. These cases arising from chorionepithelioma show several important points:

(*a*) They occur in women during their menstrual life.

(*b*) They may occur in the apparent absence of a pelvic tumour, and in the absence of most of the clinical and radiological changes usually associated with secondary carcinoma in the lungs.

(*c*) The condition, if suspected, is readily recognised by biological tests for pregnancy.

(*d*) Recent reports of the treatment of chorionic growths are encouraging and make early diagnosis important.

## Case-reports

### THE FIRST CASE

A 47-year-old housewife was admitted to the Hammersmith Hospital on May 18, 1947, and died 8 days later. She had been in good health until a year before, when she had an attack of "bronchitis", and she later developed palpitations, exertional dyspnœa, and a cough. In February, 1947, she had vaginal bleeding, and her doctor thought she had had a miscarriage. After this she had no further menstrual bleeding, and she lost weight. On May 14 she attended the medical outpatient clinic where tachycardia, slight exophthalmos, and some thyroid enlargement were noted. 2 days later she got sudden pain "all over the chest", and became acutely dyspnœic. Next day the pain was localised to the right side of the chest, and was pleuritic. There was no history of hæmoptysis. She had had four normal pregnancies, and the youngest child was 11.

*Examination*

She was a thin alert woman, with livid cyanotic facies and staring eyes. The skin was moist. She had an unproductive cough, and was very dyspnœic, the respiratory rate varying between 30 and 40 per min. The chest movements were full and equal, but the breath sounds were diminished and there were crepitations over the bases of both lungs. The pulse-rate was 120 per min. and the blood-pressure 110/70 mm. Hg. The heart was slightly enlarged to the left, and the impulse was forceful; the sounds were normal. The liver was palpable 2 in. below the right costal margin, but there was no peripheral œdema.

*Investigations*

Hæmoglobin 14·5 g. per 100 ml. Red-cell count 6 million per c.mm. 80% of the white cells were polymorphs. The erythrocyte-sedimentation rate (E.S.R.) was 8 mm. in the 1st hour (Westergren). Total $CO_2$ (May 20) 17·2 mEq. per litre. Blood-urea 60 mg. per 100 ml. Serum sodium-chloride 101 mEq. per litre. Arterial oxygen saturation (May 23) 80%. Cardiac output < 4 litres per min. (Fick method). The sputum contained a few pus cells and gram-negative bacilli. The electrocardiogram (E.C.G.) showed sinus tachycardia (May 15), and later (May 19) a pulmonale P-wave in leads II and III, with right axis-deviation. Chest X-ray (May 20) showed fine mottling in the peripheral lung fields.

*Course*

When she was seen as an outpatient some features suggested thyrotoxicosis. On admission 4 days later, however, the chest pain of sudden onset was thought to be due to multiple pulmonary emboli, and a diagnosis of acute cor pulmonale was made. Treatment with penicillin was started on May 20, and she was put in an oxygen tent. This partially relieved the cyanosis and dyspnœa. Digitalis and thiouracil were given also on May 22, but the dyspnœa and weakness increased, the venous pressure rose, and the blood-pressure fell. After calling for a bedpan she died suddenly on May 26.

*Necropsy* (Prof. C. V. Harrison)

The right auricle and ventricle were dilated and filled with clot, and the right ventricle was moderately hypertrophied. The left auricle and ventricle were rather small and empty. The lungs were fixed in situ by intratracheal injection. There was no evidence of emphysema. On cutting each lung multiple small white areas, 1–2 mm. in diameter, were seen. Closer inspection showed that these were vessels occluded by friable material. The larger vessels were patent, although two of 3–4 mm. diameter were partially occluded. The right pleura was covered with old fibrous adhesions. The uterus was slightly and uniformly enlarged, and the endometrium was smooth and of normal premenstrual thickness. The myometrium was thicker than usual but otherwise normal. At various points throughout the wall of the uterus, and especially in the cervical region, there were white areas, 2–3 mm. in diameter, resembling sclerotic vessels. On following these laterally it was found that the base of the parametrium on both sides was occupied by a mass of coiled vessels. These were distended with a thick white crumbling mass of tumour. The appearances suggested that the tumour which had metastasised to the lungs came from these parametrial veins, although the exact site of the primary tumour was uncertain.

*Histology*

*Uterus.*—Eleven blocks taken from the body and cervix showed widespread intravascular invasion by a well-differentiated chorionepithelioma. This always appeared to be within vessels. There was much more invasion of the cervix than of the body, but nowhere could an actual site of implantation be found. The endometrium showed a decidual reaction.

*Lungs.*—In every section over 80% of the vessels were occluded by a mixture of tumour and thrombus. In a few only thrombus was seen and in a minority some organisation of the thrombus had taken place. There was no invasion outside the vessels.

*Thyroid gland.*—This was somewhat hyperplastic, but was within normal limits.

THE SECOND CASE

A 19-year-old woman was admitted to St. Mary's Hospital on May 18, 1957, and died a week later. She was intensely dyspnœic and the history obtained was fragmentary. She had married at the age of 17, but had left her husband a year later. A year before admission she had consulted her doctor because of right-sided chest pain and a sore mouth. 8 months later she noticed exertional dyspnœa which rapidly became severe, and at the same time she developed a cough which was mostly unproductive, but on a few occasions there were slight hæmoptyses. Coughing had sometimes caused sharp pains in either side of the chest. She had lost 24 lb. in weight. She denied menstrual irregularity, but we learned later that a criminal abortion may have been procured or attempted, and this may have accounted for the delay in seeking medical attention.

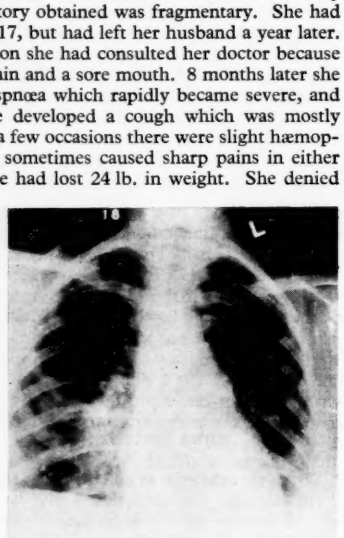


**Fig. 1—Radiograph of the second case showing changes at the base of the right lung, and slight dilation of the pulmonary artery.**

*Examination*

She was pale and slightly cyanosed with evidence of recent weight loss but without muscular wasting. At rest the respiratory rate was 30 per min., and lying flat in bed did not appreciably increase her distress. Slight exertion was followed by severe air-hunger with cyanosis of the extremities and mucous membranes. There was slight clubbing of the fingers and toes. A few rales were heard at the base of the right lung but otherwise the breath sounds were normal. The venous pressure was moderately raised, and the liver was just palpable and tender. There was slight ankle œdema. The pulse-rate was 100–130 per min. and regular. The blood-pressure was 110/70 mm. Hg. The peripheral pulses were of small amplitude. The cardiac impulse was of the diffuse right ventricular type, with a palpable shock in the 2nd and 3rd spaces just to the left of the sternum. There was a right atrial gallop rhythm, and a loud pulmonary second sound with a short systolic murmur heard over the 2nd and 3rd left spaces at the sternal border. She was menstruating at the time of admission; rectal, abdominal, and other systematic examinations revealed no abnormality.

*Investigations*

Hæmoglobin 13 g. per 100 ml. Total white-cell count 17,000 per c.mm. (polymorphs 12,000, lymphocytes 4500). Blood-cultures were negative. E.S.R. 34 mm. in the 1st hour. Chest X-ray showed diffuse shadowing at the right base; the cardiothoracic ratio was 0·5, and there was slightly increased convexity of the left cardiac border (fig. 1). E.C.G. showed a right ventricular strain pattern with T-wave inversion. Serum-sodium 130·5 mEq. per litre, serum-potassium 4·1 mEq. per litre, chloride 105 mEq. per litre, total $CO_2$ 18·4 mEq. per litre. Arterial $CO_2$ tension 16 mm. Hg. Arterial blood pH 7·5. Blood-urea 43 mg. per 100 ml.

*Course*

The patient was intermittently febrile with a terminal pyrexia of 103°F. She remained grossly dyspnœic throughout, and from the 3rd day in hospital she was cyanosed at rest despite antibiotics and digitalis. Oxygen relieved the respiratory distress noticeably at first, but during the last 2 days it was ineffective. The systolic blood-pressure was kept at over 100 mm. Hg until an hour before death. The clinical diagnosis was pulmonary hypertension with an alveolar-capillary diffusion block of unknown ætiology.

*Necropsy* (Prof. D. M. Pryce)

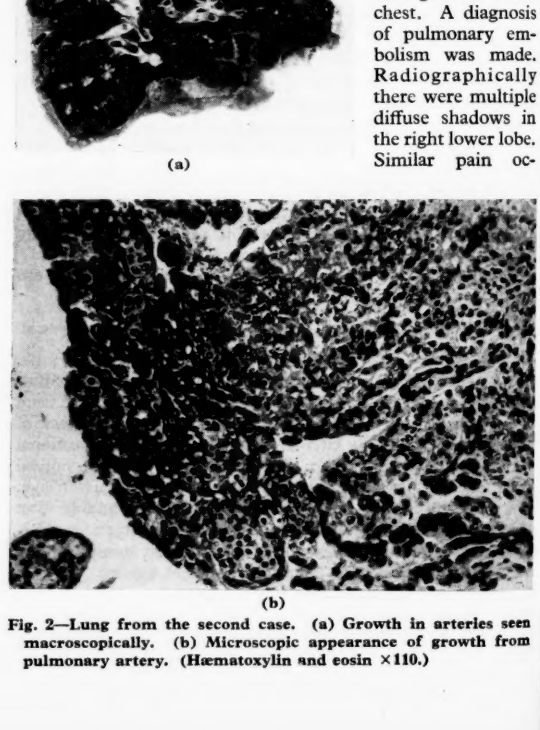
The heart was enlarged and globular because of right ventricular hypertrophy. The left ventricle was small and the valves were normal. The pleuræ showed numerous long-standing adhesions to the parietal structures. Sectioning the lungs showed that many pulmonary arteries, both large and small, were occluded by pale material with a more granular and friable structure than the usual type of thrombus. There was a wedge-shaped area of infarction (2×4 cm.) in the mid-basal segment of the right lower lobe. The uterus was a little enlarged and the os nulliparous. There was no obvious growth in the corpus uteri. The uterine and ovarian veins, and branches of the internal iliac veins, were all grossly distended and thrombosed. The ovaries were small and contained no corpus luteum. The rest of the examination was normal. No other secondary deposits were found. Microscopically there was chorionepithelioma in the pelvic veins and pulmonary arteries. No growth was found outside these vessels either in the uterus or in the lungs (figs. 2 and 3).

THE THIRD CASE

*First Hospital Admission*

A 30-year-old housewife was in good health and had had three normal pregnancies, the last in 1953. She remained well until July, 1956, when she developed irregular and heavy menstrual periods. She was admitted to St. Mary's Hospital in January, 1957, and cervical dilatation and uterine curettage was performed. The curettings showed endometrial hypertrophy only. 3 days later she had some pain, and pelvic examination revealed an abscess in the pouch of Douglas. This showed little sign of resolving with antibiotic therapy, and it was therefore drained through the anterior abdominal wall. Satisfactory healing followed. A week after the laparotomy she developed thrombophlebitis in the left leg, and on the 9th postoperative day complained of pleuritic pain in the right side of the chest. A diagnosis of pulmonary embolism was made. Radiographically there were multiple diffuse shadows in the right lower lobe. Similar pain oc-

(a)

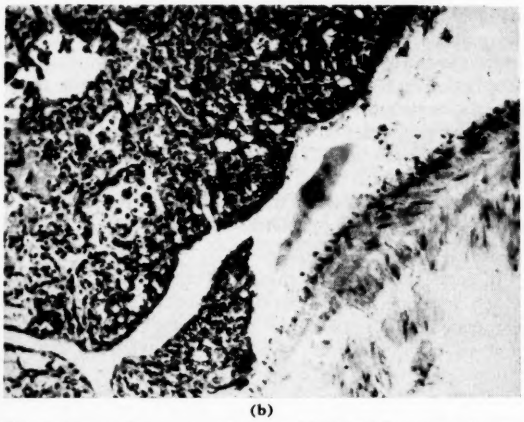


(b)

**Fig. 2—Lung from the second case. (a) Growth in arteries seen macroscopically. (b) Microscopic appearance of growth from pulmonary artery. (Hæmatoxylin and eosin ×110.)**

curred in the left side of the chest 2 days later, and she was given anticoagulants. But on the 2nd day of this treatment she took her own discharge. She attended the outpatient department in April and reported that she was quite fit. Chest radiographs at this time and in October, 1957, were normal.

(a)



(b)

**Fig. 3—Uterus from second case. (a) Sagittal section showing growth in veins. (b) Microscopic appearance of growth in uterine veins. (Hæmatoxylin and eosin ×110.)**

*Second Hospital Admission*

In April, 1958, she was readmitted because of continued menorrhagia. Hysterectomy and unilateral oophorectomy were carried out. At operation the pelvic structures were found to be normal. The uterus was examined macroscopically and microscopically because of the possibility of a perforation during the previous operation. No such evidence was found, and the uterine histology was normal. On the 10th postoperative day, left-sided pleuritic pain again occurred. Anticoagulants were withheld, but it was decided to embark on long-term anticoagulant therapy should there be evidence of further pulmonary embolism. She returned home and was well though somewhat dyspnœic on exertion.

*Third Hospital Admission*

On June 26, 1958, the patient attended hospital for abdominal-wall exercises. That evening she again had pain in the left side of the chest, followed by slight hæmoptysis and dyspnœa. She was readmitted to hospital 4 days later and transferred to a medical ward.

*Examination* revealed a moderately obese young woman who was not cyanosed, but who was slightly dyspnœic at rest. The venous pressure was slightly raised, and a shock was just discernible in the 2nd and 3rd left intercostal spaces. The character of the cardiac impulse suggested slight right ventricular enlargement. A pleural rub was heard in the left axilla. There was no clubbing and no evidence of venous thrombosis. Pelvic examination revealed no abnormality.

*Investigations.*—Hæmoglobin 12·9 g. per 100 ml. White-cell count 10,000 per c. mm. E.S.R. 40 mm. in the 1st hour. Chest X-ray showed soft diffuse shadows in the left lower zone. E.C.G. showed a slight degree of right axis-deviation.

*Course.*—Anticoagulant therapy was initiated with heparin and continued satisfactorily with phenindione. After 10 days the venous pressure had fallen to normal levels, the pleural rub had disappeared, and her general condition had improved slightly. But during the 3rd week of treatment pain recurred in the left side of the chest, and the sputum was streaked with blood. The pleural rub returned and a chest radiograph (fig. 4) showed that although the shadows in the lower zone had partially resolved, new shadows had developed in the left upper zone, and linear shadows were present in the left mid-zone. Tubercle bacilli were not found in the sputum. The E.S.R. had increased to 60 mm. in the 1st hour. A further radiograph showed a cavity-like shadow in the left upper zone. The patient developed a low-grade pyrexia. Antituberculous therapy was given for 3 weeks without notable effect on the fever. There was intermittent vomiting during this period.

6 weeks after her admission we thought the right ventricular impulse had increased and the peripheral pulses were of smaller amplitude. Slight exertion produced gross dyspnœa and central cyanosis. The E.C.G. showed increased right axis-deviation with T-wave inversion in the right ventricular leads. Oxygen administration by tent became necessary, and partially relieved the cyanosis. Because the anticoagulant therapy had failed to prevent further pulmonary embolism, a Friedman test was performed on the urine. This was positive, and was confirmed by a strongly positive result at a dilution of 1 100. The urinary gonadotrophins were estimated at >192,000 mouse uterine units (M.U.U.) per day (normal <100). The serum-electrolytes at this time were: sodium 131, potassium 4·5, chloride 89·5, and total $CO_2$ 22 mEq. per litre. The arterial oxygen saturation was 75·6% and the arterial $CO_2$ tension was 31 mm. Hg (while breathing air). The cardiac output measured by a radioisotope method was 4·5 litres per min.

*Treatment*

By the time the positive Friedman test was confirmed the patient was gravely ill; she was dyspnœic and cyanosed while breathing oxygen, and slight exertion caused extreme respiratory distress. Treatment was started with 4 amino-N-10 methyl pteroylglutamic acid ('Methotrexate') 25 mg. and 6-mercaptopurine 700 mg. daily by mouth in divided doses for 5 days. Two further similar 5-day courses of treatment have been given of intervals of 2 and 3 weeks.

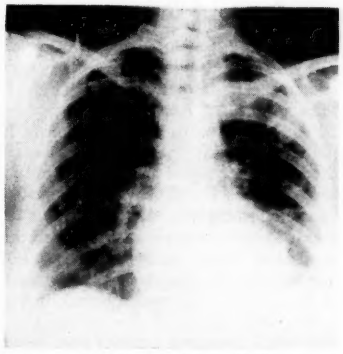


**Fig. 4—Radiograph of the third case on Aug. 25 showing minor changes in the left lung field (arterial oxygen saturation 75%).**

*Course after specific therapy.*—On the 2nd day of the first course of treatment the patient developed more bilateral pleuritic pain, and a radiograph showed numerous new opacities particularly in the right lung. We concluded that further emboli had been thrown off, possibly as a result of treatment Her condition afterwards improved rapidly. Oxygen therapy was discontinued the day after completing the first course of treatment. 3 days later she was allowed out of bed, and she was able to walk a few paces without dyspnœa. The arterial oxygen saturation 12 days after the end of the first course of treatment had risen to 95%. Cardiac catheterisation at this time showed a right ventricular pressure of 50/0 mm. Hg. The cardiac output was 5·5 litres per min. (Fick method). A chest radiograph on the same day showed almost complete clearing of the pulmonary lesions.

Since the second and third courses of treatment the patient has been at home leading a normal life, and she is now in

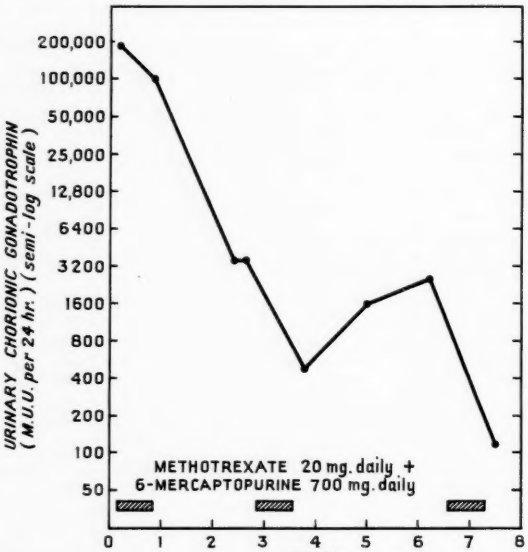



**Fig. 5—Gonadotrophin excretion in the third case during therapy.**

complete clinical and radiographic remission. The urinary gonadotrophin level fell to 50 M.U.U. after the third course, and we propose to give further courses should it rise again (fig. 5).

Repeated E.C.G.s have shown a gradual lessening of the changes due to right ventricular strain.

*Toxic effects.*—During the first course of treatment mild proteinuria persisted for 7 days, but did not recur during the later courses. The bromsulphalein test showed a pretreatment figure of 17% retention at 25 minutes. After the first course this rose to 23% but later levels were lower, and after the third course the figure had fallen to 11%. During each course the hæmoglobin fell from 12·9 g. per 100 ml. to about 11 g. per 100 ml., but returned spontaneously between courses to the higher level. At the same time severe oral and pharyngeal ulceration developed and presumably extended throughout the intestinal tract. This was treated with a semifluid diet, anæsthetic lozenges, and frequent mouth washes. There was vomiting and nausea at first, but this ceased when chlorpromazine 25 mg. daily was given. Folliculitis and ulceration occurred in the skin especially around the anus; irritation was at times severe, but was relieved by very small applications of a wax-base ointment containing 1% folic acid. A diffuse alopecia of moderate severity also developed during treatment. The toxic effects were most severe 2 to 5 days after completing each course of treatment, and recovery occurred in the following 10 days.

## Discussion

The presentation of neoplastic disease with metastases in the lungs is all too familiar. The site of the primary tumour may be difficult to determine during life, but the radiographic appearances of the pulmonary lesions and other diagnostic features usually reveal the true nature of the illness. By contrast, the cases described here presented as cardiorespiratory problems with little or no radiographic evidence of pulmonary metastases, and with scant evidence to suggest the site of the primary tumour, or indeed to suggest that the disease was neoplastic.

Novak and Seah (1954) found that chorionepithelioma followed 1 in every 200,000 pregnancies. In half of these the growth followed a full-term pregnancy, and the other half followed in equal numbers a miscarriage or decidual mole. The high incidence of pulmonary metastases in chorionepithelioma is well recognised, and the presence of tumour emboli in these metastases was reported long ago by Schmauch (1907). Their presence, without evidence of pulmonary invasion, on such a scale as to lead to right ventricular failure and death from anoxia, has not been widely noted.

Some of the vagaries of chorionepithelioma have aroused attention, and failure to find a primary growth in the uterus even on careful microscopic examination is not infrequent (e.g., Brown et al. 1940). One can only speculate as to whether this is due to malignant transformation of normal chorion which has entered the uterine veins, or to regression of a tumour previously present in the uterus. Since normal chorionic tissue may embolise to the lungs in normal pregnancy, the presence of this tissue in blood-vessels cannot be regarded as evidence of malignancy per se. But the histological appearances of the material found in the pelvic veins and pulmonary arteries in the first two cases was regarded as unequivocally neoplastic, and the lack of wider invasion from these growths is therefore surprising. Clearly, this failure may be due to properties of the tumour itself, or to the resistance of host tissues. The fact that these tumours are fœtal in origin, and hence potentially capable of provoking an antigenic response in the maternal host, could have some bearing on this problem.

*Summary of Clinical Findings*

In each patient the dominant symptom was dyspnœa, which developed over a period of months and which was aggravated in a remarkable way by slight exertion. By contrast, it was noted in two of them that lying flat without pillows did not increase the dyspnœa unduly. Pleuritic pain was a late feature in one patient but was recurrent over periods of 12 and 18 months in the other two.

The duration of the illness is difficult to estimate because of the intermittent nature of the symptoms in the early stages. The first and second patients developed respiratory symptoms a year before presentation and had been very ill for more than 3 months. The third patient first had a pulmonary embolus 18 months before diagnosis, but this may have been secondary to thrombophlebitis in the leg.

Recurrent small hæmoptyses (usually just streaking of the sputum) occurred in two cases. Weight loss was reported by all three, but only one patient was wasted. The menstrual history was in no way characteristic although in two patients menstrual disorders were, or had been, present.

There was central cyanosis in each case, and like the dyspnœa this was notably increased by exertion and relieved partially by oxygen therapy. The peripheral pulses were of small amplitude, and the low cardiac output was confirmed in two cases. There was clinical evidence also of pulmonary hypertension, with right ventricular enlargement and failure of mild to moderate severity. E.C.G.s consistently showed the appearances of right ventricular strain. There was slight clubbing in one case, but examination of the chest was remarkable chiefly for the paucity of signs in relation to the degree of dyspnœa and cyanosis.

The chest radiograph in the first case showed slight peripheral mottling, and in the second case a few days before death it showed only localised shadows in the lower right lung field. Serial radiographs in the third case showed multiple soft opacities each of which rarely persisted for more than 2 weeks, and linear shadows of the type often associated with pulmonary embolism. A cavity, 2 cm. in diameter, appeared in one upper-lobe lesion and persisted for 6 weeks (fig. 4). The radiographs also confirmed the presence of right ventricular enlargement and pulmonary-artery dilatation in two of the patients.

The sedimentation-rates varied between 8 mm. in the 1st hour and 108 mm. In all cases the blood-electrolyte picture showed a respiratory alkalosis, but in the third case this was modified by the metabolic disturbance of vomiting and ketosis. The arterial oxygen saturation was 80% and 76% in the two cases in which it was measured. The hæmoglobin level was normal or slightly reduced, and each patient had a polymorphonuclear leucocytosis, but in one this was not marked. All three patients were periodically febrile during their stay in hospital, and the fever did not respond to antibiotics.

*Differential Diagnosis*

Of the three cases described, only one was diagnosed during life and that was after considerable delay. The presence of pulmonary hypertension was correctly deduced clinically in all three.

In the first case thyrotoxicosis was a possible cause for part of the clinical picture, and pulmonary embolism was suspected as the cause of the chest pain. In the second case a right-to-left intracardiac shunt was considered, but substantiating evidence was not obtained, and the notable initial lessening of the cyanosis by oxygen administration made a shunt mechanism unlikely. The low arterial oxygen saturation together with the low arterial $CO_2$ tension and absence of severe radiographic abnormalities in the chest suggested the existence of an alveolar-capillary diffusion block (Baldwin et al. 1949).

From the necropsy findings in the first two cases, where over 80% of the pulmonary arterial bed was occluded, it was evident that the defect was primarily a failure of vascular perfusion resulting in a gross reduction of the effective diffusion area of the lungs, and not a diffusion "barrier". The low cardiac output must also result from the gross reduction of the pulmonary vascular bed, and the severity of the dyspnœa on slight exertion from an inability to increase the cardiac output appreciably above the resting level.

Distinction from simple emphysema was not difficult clinically; moreover the blood-gas picture contrasted with the carbon-dioxide retention of that condition. Difficulty in distinguishing between pulmonary tuberculosis and the pulmonary manifestations of chorionepithelioma was noted over 50 years ago (Kelly and Teacher 1898), and in the third case the radiographic features mimicked tuberculous changes sufficiently to lead to the administration of antituberculous drugs.

The main problem arises in distinguishing these cases from those of subacute thromboembolism, especially where this follows pregnancy. Since the basic mechanisms in the two conditions are similar, distinction in the absence of a pelvic tumour will be possible only by means of biological tests for gonadotrophic activity. It therefore seems desirable to perform such a test in all cases of thromboembolism in women of menstrual age.

The possibility of positive tests arising from pregnancy, the menopause, benign chorionic growths, or pituitary tumours must of course be borne in mind. Positive tests at a urinary dilution of 1/100, or preferably quantitative tests of urinary gonadotrophins are desirable as confirmation. Zondek (1942) regarded an excretion of more than 200,000 M.U.U. daily as diagnostic of chorionic growths, but levels exceeding this have been reported in the first 3 months of pregnancy (Hobson 1955). Nevertheless the quantitative test when used in conjunction with the clinical and pathological findings, as in Delfs' (1957) study, is a most useful aid to diagnosis and the most sensitive guide in therapy (Li et al. 1958).

The presentation with subacute pulmonary hypertension of two cases of latent chorionepithelioma within a period of 14 months under the care of one physician suggests that the condition may be less rare than the literature indicates. Such cases may have been diagnosed as thromboembolism or as idiopathic pulmonary hypertension both clinically and in the postmortem room.

*Treatment*

Interest in these tumours, which are usually rapidly progressive, has been heightened by reports of new methods of treatment.

Radiotherapy in general has been disappointing, but some prolongation of life has probably resulted from the use of nitrogen mustard and its derivatives (Beecham et al. 1955, Ishizuka 1956).

Because chorionic tumours are fœtal in origin and therefore of different genetic structure from the maternal tissues, an interesting new approach has been made by Doniach et al. (1958), who transferred tissue from the husband to the patient with the object of increasing her antigenic response to the tumour cells.

Hertz et al. (1958) have described the treatment of 27 women with chorionic growths by interrupted high-dose anti-folic-acid and anti-purine drugs. 5 of them survived for 8 to 29 months in complete clinical, radiological, and hormonal remission at the time of reporting, and 7 others were in complete clinical but incomplete hormonal remission. 1 patient died apparently from the hepatotoxic effects of the drugs. Our patient has been treated by the regime described by these workers, and has made a gratifying initial response although she was gravely ill when it was begun. Holland (1958) has reported another case treated successfully by the same method. It is clearly far too early to assess the long-term prognosis. Careful clinical, hæmatological, hepatic, and renal assessment is essential during treatment. In our patient the drug-induced nausea and vomiting were effectively controlled by small doses of chlorpromazine, and the skin ulceration by folic-acid ointment (1%) applied sparingly to the ulcers only. Larger quantities might lead to absorption of a significant amount of folic acid through the skin and interfere with the therapeutic action of the drugs.

## Summary and Conclusions

Two young women who presented with dyspnœa, cyanosis, pulmonary hypertension, and low cardiac output were found at necropsy to have chorionepithelioma confined to the pelvic veins and pulmonary arteries.

A further patient has similar clinical features and a high gonadotrophin titre, and is thought to have a similar pathological process, though neither diagnostic curettage nor careful histological examination of the uterus showed the presence of chorionepithelioma.

The diagnostic difficulties, and the pathological and hæmodynamic features of these cases are discussed.

The diagnosis of subacute thromboembolism or of idiopathic pulmonary hypertension should not be made in women of menstrual age without exclusion of chorionepithelioma by means of a biological pregnancy test.

The one patient in this group diagnosed during life has made a very remarkable response to treatment with anti-folic-acid and anti-purine drugs in high intermittent dosage.

We are indebted to Prof. Russell Fraser for kindly allowing us to publish the details of the first case, and to Professor Harrison and Professor Pryce for the necropsy findings. We also wish to thank Dr. I. F. Sommerville for the frequent gonadotrophin estimations, and Mr. A. Beasley for the photomicrographs. The 'Methotrexate' was supplied by Lederle Laboratories.

## Addendum

After we completed the above report, a woman of 28 under the care of Sir George Pickering at the Radcliffe Infirmary, Oxford, was found to have the same condition

and was transferred to St. Mary's Hospital under the care of Prof. W. S. Peart. This patient had the classical features of " idiopathic " pulmonary hypertension without any clinical or radiological evidence of pulmonary embolism or infarction, and the only gynæcological abnormality was a slight menstrual irregularity since the birth of a child 2 years ago. The cardiac output at rest was 2·5 litres per min., and it rose after exercise to 4·0 litres per min. The urinary gonadotrophins were estimated at > 100,000 mouse uterine units per day. Therapy on the above-mentioned lines was started; after 3 months the gonadotrophin excretion has fallen to normal, and the pulmonary hypertension has lessened somewhat.

We are grateful to Sir George Pickering and Professor Peart for permission to quote this case.

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# METABOLISM OF MYELIN: THE PERSISTENCE OF (4-$^{14}$C) CHOLESTEROL IN THE MAMMALIAN CENTRAL NERVOUS SYSTEM

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IN the course of studies on myelination, it was shown (Davison, Dobbing, Morgan, and Payling Wright 1958) that it is possible to incorporate labelled cholesterol into the brain of the developing chicken by injecting this substance into the residual yolk-sac on the day of hatching. It was also then shown that a large proportion of the labelled cholesterol persisted in the brain for as long as six months, and subsequent observations have shown that in other birds of the same experimental group the quantity present fourteen months after its administration has undergone little further decline.

The successful incorporation into the central nervous system of the radioactive cholesterol, which reached a maximum at about 30 days and fell to a more constant and persistent level after about 100 days, led us to suggest that the metabolic processes that involve brain cholesterol may take place at different rates in different morphological compartments of the central nervous system. " Were it possible ", we stated, " to dissociate the myelin from the cells, the cholesterol might be found to persist even longer in the former than in the latter ".

In an attempt to throw further light on the durability of this important lipid component of myelin in the central nervous system, a more extensive long-term experiment lasting twelve months has been undertaken on developing rabbits. This change of species has made it possible to extend the earlier findings in two directions: (1) it supplements the former observations on chickens with comparable ones on a mammal; and (2) it amplifies them by taking advantage of the larger brain of the rabbit to study any differences that might appear in the retention of the labelled cholesterol in the grey and white matter.

The general conclusions reached in the present work are fully consistent with those drawn from the previous study on chickens.

## Materials and Methods

The technique for preparing the cholesterol emulsion for injection and the procedures both for the quantitative estimation of cholesterol in the tissues and for the assay of its radioactivity in the final digitonide precipitate have already been described (Davison et al. 1958).

The thirteen rabbits used formed two litters of the same strain (Copenhagen Whites), and were born on the same day and reared in identical fashion. Each received a single intraperitoneal injection of 5 μc (4-$^{14}$C) cholesterol in 0·25 ml. emulsion on the 17th day after birth. At this age, myelination is proceeding rapidly.

Single animals were killed with intravenous pentobarbitone at roughly equal intervals; on the 12th and 365th days, two were killed to provide duplicate analyses. The cholesterol estimations and the assays of the radioactivity were performed on extracts from each brain (see below), spinal cord, heart, liver, kidneys, and plasma. In several of the later rabbits, pieces of sciatic nerve were also removed and extracted in a similar manner for analysis and counting.

The brains were fixed entire in formol-saline for 24 hours to harden them and then dissected into " grey " and " white " fractions. The dissection was performed by cutting the whole brain from before backwards into coronal slices each about 2 mm. thick. Each slice was then separated as far as possible into grey and white matter. A fairly clean separation was not difficult for most of the cerebrum and cerebellum, but in those regions in which there was no clear anatomical demarcation between grey and white matter no separation was attempted and equal portions were allotted to the " grey " and " white " specimens. The predominantly white medulla oblongata was given mainly to the " white " specimen. The resulting specimens, hereafter referred to as " grey " and " white ", together comprise the whole brain, but each fraction is inevitably considerably contaminated by the other. After dissection, the two specimens were treated for cholesterol estimation and radioactivity assay in the same way as were the other organ samples.

To render the assays on the " grey " and " white " specimens better comparable with each other, their radioactivities were also expressed as specific activities (counts per minute per mg. cholesterol) since with such dissected fragments the " whole organ " cannot be defined. Moreover, to compensate for the growth of the animals during the course of the experiment, these specific activities have been corrected (using the 12th-day cholesterol estimates as the reference value) for the natural increment in this myelin lipid during this lengthy period.

## Results

The amounts of cholesterol and of labelled cholesterol present in the brain, spinal cord, heart, liver, kidneys, and plasma are set out in table I and fig. 1; the former are expressed as mg., the latter as counts per minute, for the whole organ or per ml. of plasma. From these results three conclusions emerge: (1) that during the early stages

of development the rabbit can incorporate parenterally administered cholesterol into its central nervous system; (2) that this substance is taken up more slowly by the brain and spinal cord than by the three other organs studied; and (3) that the incorporated labelled cholesterol is retained in the central nervous system for at least 12 months, and probably for much longer. Nor did this retained cholesterol appear to undergo any metabolic transformation while present in the central nervous system. For when radioactive cholesterol isolated from the brains of these rabbits 12 months after their injection was converted into the corresponding keto acid through the removal of carbon atom four by mild oxidation, all radioactivity was lost, so demonstrating that all the persistent radioactive cholesterol recovered had retained its $^{14}C$ label in the original 4-C position (Davison and Wajda 1959).

TABLE I—CHOLESTEROL CONTENT AND RADIOACTIVITY OF VARIOUS ORGANS AT VARIOUS INTERVALS AFTER INJECTION OF (4-$^{14}C$) CHOLESTEROL INTO 17-DAY-OLD RABBITS

| Day after injection | Central nervous system | | Heart | Liver | Kidneys |
|---|---|---|---|---|---|
| | Brain | Spinal cord | | | |
| | Cholesterol (mg. per whole organ) | | | | |
| 12 | 90·7* | 36·3* | 2·1* | 44·1* | 18·3* |
| 26 | 116·3 | 59·1 | 2·3 | 23·4 | 23·6 |
| 41 | 157·2 | 82·6 | 4·3 | 112·9 | 44·3 |
| 68 | 150·3 | 142·2 | 5·6 | 137·4 | 44·1 |
| 103 | 170·7 | 179·3 | 4·5 | 129·9 | 48·2 |
| 131 | 206·1 | 228·3 | 5·8 | 156·1 | 50·6 |
| 173 | 176·1 | 232·0 | 6·4 | 226·9 | 53·0 |
| 216 | 212·1 | 242·6 | .. | .. | .. |
| 257 | 185·5 | 231·0 | .. | .. | .. |
| 341 | 229·0 | 245·0 | .. | .. | .. |
| 365 | 189·7* | 248·3* | .. | .. | .. |
| | Radioactivity (c.p.m. per whole organ) | | | | |
| 12 | 718* | 133* | .. | 2040* | 2277* |
| 26 | 1007 | 210 | 325 | 1090 | 1260 |
| 41 | 629 | 105 | 51 | 608 | 687 |
| 68 | 405 | 147 | 19 | 70 | 220 |
| 103 | 508 | 152 | 7 | 92 | 50 |
| 131 | 612 | 206 | 5 | 46 | 12 |
| 173 | 369 | 167 | 2 | 60 | 15 |
| 216 | 283 | 103 | .. | .. | .. |
| 257 | 363 | 193 | .. | .. | .. |
| 341 | 278 | 123 | .. | .. | .. |
| 365 | 268* | 175* | .. | .. | .. |

* Averages from two rabbits.

The amount of radioactive cholesterol recovered from the spinal cords underwent no sensible change throughout the whole 12 months of the experiment. In this respect, the spinal cord gave results that resembled those of the " stable " compartment (see below) of the brain; and this, as can be seen from fig. 2, was located mainly in the white matter.

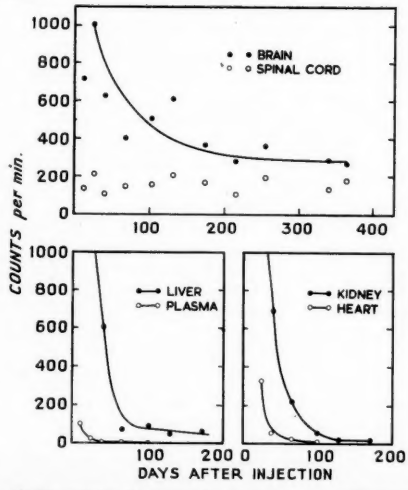


**Fig. 1—Radioactivity (expressed as counts per minute per whole organ or per ml. plasma) in the brain, spinal cord, heart, liver, kidneys, and plasma at various intervals after the injection of (4-$^{14}C$) cholesterol into 17-day-old rabbits.**

TABLE II—SPECIFIC ACTIVITY (C.P.M. PER MG.) OF CHOLESTEROL IN SCIATIC NERVES AT VARIOUS TIMES AFTER INJECTION

| Days after injection | Specific activity |
|---|---|
| 131 | 3·9 |
| 216 | 1·9 |
| 257 | 2·2 |
| 341 | 2·2 |
| 365 | 1·9 |

From the other results set out in table I and fig. 1, it can be seen that the metabolic turnover of cholesterol in the heart, liver, and kidneys is strikingly different from that in the brain and spinal cord. These three organs not only take up the labelled cholesterol more rapidly than the central nervous system, but also fail to retain it in the same way. Within a few weeks, most of it had disappeared, and by the end of four or five months, these organs had lost it completely.

From a limited number of observations made on sciatic nerves (see table II), it would seem that in durability their cholesterol resembles that of the central nervous system. From the 7th month to the end of the experiment at 12 months, the specific activity of their cholesterol showed no significant change.

For the first 4 or 5 months the labelled cholesterol in the brain steadily diminished, but during the second half of the experimental period the rate of decrease was perceptibly slower and might end finally at some stable level. This result seems explicable when the radioactivities of the " grey " and " white " portions of the brain are determined separately (see fig. 2). From the results set out in fig. 2, it appears that the " turnover-rate " for cholesterol differs materially in these two portions of the brain.

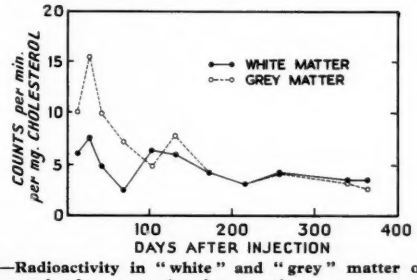


**Fig. 2—Radioactivity in " white " and " grey " matter of brain (expressed, after correction for growth, as counts per minute per mg. cholesterol) at various intervals after the injection of (4-$^{14}C$) cholesterol into 17-day-old rabbits.**

That in the " white " matter is barely perceptible throughout the whole 12 months of the experiment, while that in the " grey " seems to have two phases: in the first, which lasts several months, it is comparatively active, whereas in the second it is little different from that observed for the " white " matter throughout. Two features of " white " matter—first its relatively much lower metabolic activity, and secondly its much greater content of myelinated fibres—suggest that this " stable compartment " may represent the cholesterol in the nerve-sheaths.

## Discussion

One of the most crucial questions in the pathogenesis of the demyelinating diseases is the durability of the myelin-sheaths under normal conditions in the adult central nervous system. Do these sheaths have a high

degree of permanence, comparable with that of collagen fibres (see Neuberger et al. 1951), or do they ordinarily undergo continuous maintenance throughout life through the agency of specialised neuroglial cells?

Several different experimental findings now support the belief in the relative permanence of the normal nerve-sheath. These include both our earlier (1958) and our present study on the persistence of (4–$^{14}$C) cholesterol, the work of Davison and Dobbing (1958) on $^{32}$P-labelled phosphate incorporated into brain phospholipids, and the study of Davison, Morgan, Wajda, and Payling Wright (1959) on (3–$^{14}$C) serine incorporation into other myelin lipids.

When labelled cholesterol is injected parenterally into rabbits while their central nervous system is still developing, much of the fraction that enters the brain and spinal cord remains in them long after it has disappeared from the blood and the three other organs examined. Although its persistence in the central nervous system as a whole for a long time when compared to the lifetime of this species contrasts with its progressive loss from the other organs, the gradual decline in the first few months shows that even in the brain some metabolic loss takes place. The observation that during this earlier period the specific activity of the cholesterol in the "grey" matter tends to fall, while that in the "white" undergoes little change, may help to explain the decline recorded for the organ as a whole. It is known that the oxygen consumption of the grey matter of the brain is much larger than that of the white (Elliott and Heller 1957), and the greater decline in the labelled cholesterol in the "grey" matter of the rabbits during this period may be related to this difference in metabolic activity. Once this metabolic loss has ended, the durability of the remaining labelled cholesterol might be expected to be more nearly equal in all parts of the brain.

The present results accord well with inferences as to the elaborate internal structure of the myelin-sheath which have been drawn from recent observations made by electron microscopy and other biophysical methods (see Finean and Robertson 1958). From these studies it seems probable that the cholesterol molecules in this structure form an important radially arranged component in the numerous protein-lipid laminæ whose successive laying down during embryogenesis creates the definitive myelin-sheath. It seems unlikely that molecules so uniformly aligned and embedded in the interior of the sheath could be readily exchangeable and form part of an active metabolic pool; this doubt is strengthened by the finding that the site of radioactive labelling at carbon atom four of the injected cholesterol undergoes no change during its presence for 12 months in the rabbit's brain. Rather, it would appear that, once laid down in these complex laminæ, the myelin lipids, cholesterol among them, remain for long periods, perhaps indefinitely, at the site of their deposition during the developmental phase of the central nervous system.

**Summary**

Radioactive (4–$^{14}$C) cholesterol was injected into 17-day-old rabbits—an age when myelinisation in the central nervous system is proceeding.

In animals killed at various times up to 365 days subsequently, the labelled cholesterol was found to persist in the central nervous system although it had disappeared within the first few months from the heart, liver, kidneys, and plasma.

In the central nervous system the degree of persistence of the labelled cholesterol differed in the "grey" and "white" matter; in the former there was evidence of "turnover" during the first few months, while in the latter there was little indication that this substance, once incorporated, was later lost.

The radioactive cholesterol recovered from the brain 365 days after its injection still retained its radioactive carbon atom at the original 4-C position.

From these and other related observations, it seems that the myelin lipids may remain indefinitely in the nerve-sheaths where they were laid down originally during the development of the central nervous system.

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## DIURNAL FLUCTUATION OF PLASMA-FIBRINOLYTIC ACTIVITY IN NORMAL MALES

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WHILE examining the action of various substances which, by increasing the fibrinolytic activity of the plasma, might be useful in the treatment of thromboembolic disease, we found that there is a physiological increase of fibrinolytic activity in normal ambulant males during the morning. This finding shows that, in assessing the effect of procedures designed to increase fibrinolytic activity, allowance must be made for spontaneous fluctuation, and it adds to the growing list of biological phenomena with a diurnal rhythm.

### Material and Methods

Two groups, each of 10 subjects, were examined on 3 occasions by two methods.

The younger subjects (group 1) were healthy male medical students, aged 20 to 24. 7 additional young subjects were examined by one method only. The older men (group 2) came from nearby business establishments and their ages ranged from 38 to 50; they had no past history suggestive of arterial disease or hypertension, and were not having any medical treatment at the time of the experiment. Most subjects attended the laboratory on 2 consecutive days, adhering as strictly as possible to the same timetable each day. They had breakfast containing no fatty foods or eggs (cereal with stewed fruit, dry toast with honey or marmalade, and black coffee or tea without milk). The first blood sample (sample 1) was taken between 8.50 and 10 A.M., and sample 2 was withdrawn 3 hours later. Sample 3 was obtained next morning at the same time of day as sample 1. In subjects 15 and 16 there was 24 hours' interval between the control and test days.

Plasma fibrinolytic activity was determined by Bidwell's (1953) method, as described by Biggs and Macfarlane (1957), and the euglobulin lysis-time was measured by the method described by Buckell (1958). All blood and plasma specimens were kept in melting ice. Plasma was separated at 3000 r.p.m. for 10 minutes at 0–4°C in a refrigerated centrifuge, and the estimations were started immediately afterwards.

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TABLE I—FIBRINOLYTIC ACTIVITY OF NORMAL MALES AGED 20–24 (GROUP 1)

| No. | Age (yr.) | Euglobulin lysis-time (min.) | | | Plasma fibrinolysis: % lysis after 6 hours | | | Plasma fibrinolysis: % lysis after 24 hours | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | Sample 1 | Sample 2 | Sample 3 | Sample 1 | Sample 2 | Sample 3 | Sample 1 | Sample 2 | Sample 3 |
| 1 | 21 | 104 | 84 | 128 | .. | .. | .. | .. | .. | .. |
| 2 | 22 | 180 | 90 | 208 | .. | .. | .. | .. | .. | .. |
| 3 | 24 | 160 | 92 | 158 | .. | .. | .. | .. | .. | .. |
| 4 | 21 | 189 | 94 | 138 | .. | .. | .. | .. | .. | .. |
| 5 | 22 | 145 | 122 | 238 | .. | .. | .. | .. | .. | .. |
| 6 | 21 | 90 | 82 | 127 | .. | .. | .. | .. | .. | .. |
| 7 | 22 | 192 | 152 | 171 | .. | .. | .. | .. | .. | .. |
| 8 | 22 | 278 | 128 | 277 | 0 | 25·5 | 0 | 23 | 100 | 38 |
| 9 | 21 | 110 | 85 | 90 | 0 | 100 | 98 | 100 | 100 | 100 |
| 10 | 21 | 289 | 103 | 110 | 0 | 78 | 61 | 100 | 100 | 100 |
| 11 | 20 | 97 | 50 | 108 | 95 | 100 | 78 | 100 | 100 | 100 |
| 12 | 23 | 121 | 60 | 140 | 20 | 100 | 4 | 95 | 100 | 38 |
| 13 | 22 | 286 | 146 | 110 | 0 | 0 | 22 | 6·5 | 92 | 100 |
| 14 | 20 | 190 | 81 | 115 | 0 | 3·5 | 9·5 | 36 | 100 | 86 |
| 15 | 20 | 140 | 80 | 140 | 12 | 96 | 12 | 95 | 100 | 100 |
| 16 | 21 | 368 | 179 | 324 | 0 | 0 | 0 | 15 | 97 | 16 |
| 17 | 21 | 163 | 53 | 250 | 35 | 97 | 0 | 100 | 100 | 89·5 |
| Average | 21·5 | 182·5 | 98·9 | 166·5 | 16·2 | 60 | 28·4 | 67·05 | 98·9 | 76·7 |

## Results

Details of the fibrinolytic activity of the 27 men examined are given in tables I and II.

*Increase of Activity during the Morning* (Samples 1 and 2 compared)

In all the 27 pairs of euglobulin-lysis-time estimations there was an increased activity in the midday specimen compared with that found 3 hours earlier. In the Bidwell estimations, the percentage lysis after 6 hours' incubation was greater in the second specimen in 16 out of 20. In the other 4 subjects there was no lysis at 6 hours in either specimen, but all 4 showed an increase in the 24-hour lysis. In both groups the increase in activity by either method is highly significant at the level of $P=0.001$.

*Effects of Age*

The increase of fibrinolytic activity during the morning was greater in the younger than in the older group. With Bidwell's method, the amount of lysis at 6 hours was greater in all 3 samples in the younger than the older group, but application of the *t* test shows that only the 6-hour lysis in sample 2 is significant at the $P=0.01$ level. On the other hand the lysis-times for comparable specimens in the two age-groups estimated by the euglobulin method, and the values for the 24-hour period by Bidwell's method are both very similar.

TABLE II—FIBRINOLYTIC ACTIVITY OF NORMAL MALES AGED 38–50 (GROUP 2)

| No. | Age (yr.) | Euglobulin lysis-time (min.) | | | Plasma fibrinolysis: % lysis after 6 hours | | | Plasma fibrinolysis: % lysis after 24 hours | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | Sample 1 | Sample 2 | Sample 3 | Sample 1 | Sample 2 | Sample 3 | Sample 1 | Sample 2 | Sample 3 |
| 18 | 38 | 303 | 171 | 333 | 0 | 0 | 0 | 0 | 94 | 34 |
| 19 | 42 | 175 | 110 | 290 | 0 | 0 | 0 | 26 | 83 | 9 |
| 20 | 38 | 120 | 99 | 112 | 0 | 10·5 | 9 | 97 | 100 | 100 |
| 21 | 38 | 88 | 71 | 85 | 23 | 36·5 | 38·5 | 100 | 100 | 100 |
| 22 | 50 | 183 | 102 | 185 | 5·5 | 11 | 6 | 100 | 100 | 100 |
| 23 | 45 | 253 | 163 | 198 | 0 | 4 | 1 | 58 | 100 | 88 |
| 24 | 45 | 230 | 133 | 192 | 0 | 3·5 | 0 | 37 | 100 | 85 |
| 25 | 49 | 145 | 103 | 140 | 7 | 10 | 12 | 100 | 100 | 100 |
| 26 | 38 | 110 | 74 | 115 | 11·5 | 10·5 | 0 | 100 | 100 | 88·5 |
| 27 | 45 | 121 | 74 | 114 | 3 | 34 | 0 | 100 | 100 | 83 |
| Average | 42·8 | 172·8 | 110 | 176·4 | 5 | 12 | 6·6 | 71·8 | 97·7 | 78·7 |

*Fibrinolytic Activity at Comparable Times on Successive Days*

Despite a determined attempt to keep environmental conditions the same on the 2 days of the experiment, and a carefully standardised analytical procedure, there was considerable variation between fasting specimens taken on successive mornings from the same subject. This variation is not statistically significant for the euglobulin lysis-times or for the 24-hour plasma fibrinolysis, but is significant for the 6-hour plasma fibrinolysis in both age-groups.

## Discussion

The consistent rise of fibrinolytic activity over a 3-hour period in the morning, coupled with the return to a low level the following morning, confirms the demonstration by Fearnley et al. (1957) of a diurnal fluctuation of fibrinolytic activity. Testing groups of day and night nurses at 4 A.M. and 4 P.M., they found greater fibrinolytic activity by day than by night, regardless of which shift the nurses were on. They also made repeated observations in 2 subjects over a 24-hour period and found a morning increase in fibrinolysis which was maximal at about midday; this level was maintained in the afternoon, and gradually fell to a minimum at about 4 A.M. Unfortunately no details are given of sampling in relation to meals. Such data are important in view of the demonstration by Greig (1956), which we have confirmed (p. 662), that a meal containing animal fats may inhibit fibrinolysis and thus mask a physiological increase during the hours following such a meal.

The natural increase of fibrinolytic activity during the morning has to be considered when evaluating the response to drugs and experimental procedures. For example, Greig's (1957) finding that vegetable fat sometimes appears to increase fibrinolysis may be based on the assumption (shared by most workers in this field) that the baseline activity remains constant.

The considerable differences of fibrinolytic activity of plasma taken from the same person at the same time on different days—illustrated by cases 5, 10, and 13—shows the need for multiple observations under standard conditions before deciding what is normal for any individual. There is evidence that fibrinolytic activity may be increased by fear, strenuous exertion, operations, and menstruation; but, since none of these factors operated in our series, we conclude that there are other unrecognised factors which can influence the titre to a very considerable extent.

Our study of the influence of age on fibrinolytic activity is incomplete inasmuch as no observations have been made on persons over 50. It would be interesting to know whether the increased tendency to thromboembolic disease with advancing years is correlated with an intermittent or sustained depression of fibrinolytic activity. After coronary thrombosis, Hume (1958) found that such activity was reduced for about 8 days, rising thereafter to a more "normal" level, and Witte (1956) reported a decrease in the level of proenzyme in the plasma. Unfortunately the opportunity of estimating the proenzyme level and the fibrinolytic activity before and after infarction in the same subject is unlikely to arise, and the problem cannot be solved by animal experiments since the surgical trauma involved in producing coronary occlusion would itself change the level of fibrinolytic activity.

## Summary

In all of 27 normal male subjects there was a spontaneous increase in fibrinolytic activity over a period of

3 hours during the morning. Next morning the titre had returned to a low level.

The increase during the morning was greater in 17 subjects aged 20–24 than in 10 subjects aged 38–50.

The average level of fibrinolytic activity was higher in the younger group.

In some subjects there was a considerable difference in fibrinolytic activity under comparable conditions on successive mornings.

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## EFFECT OF BUTTER LIPÆMIA ON THE RATE OF CLOT LYSIS IN NORMAL MALES

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IN the preceding article we showed that the fibrinolytic activity of plasma, which is partly responsible for the removal of intravascular clots, increases during the morning. Both the early-morning level of activity and the size of the morning increase were less in men aged 38–50 than in men of 20–24. We now compare the effect of a fatty meal on the fibrinolytic activity of the same two age-groups.

### Materials and Methods

The method used and the composition of the 2 groups were the same as before. The same procedure was followed next day (samples 3 and 4), but 50 g. of butter on fat-free unsweetened biscuits was eaten after the 9 A.M. sample had been withdrawn. Therefore, in the tables which follow, sample 2 was taken at noon on the first day, and sample 4 at noon on the second day, 3 hours after a fatty meal. Samples 1 and 3 were both taken at 9 a.m. on consecutive days, and these results are presented in the previous paper.

### Results

The fibrinolytic activity of low-fat and lipæmic plasma from each man is shown in tables I and II. Because of the normal morning increase in fibrinolytic activity, a specimen taken before the fat was eaten could not be used as a control. The use as control to the lipæmic samples of specimens taken at the same time on the previous day assumes that the activity at a given time is the same on consecutive days. As we have already shown, this is not always so; but this method of control is preferable because it attempts to take the diurnal fluctuation into account.

TABLE I—EFFECT OF LIPÆMIA ON FIBRINOLYTIC ACTIVITY IN THE BLOOD OF NORMAL MALES AGED 20–24

| | | Euglobulin lysis-time (min.) | | Plasma fibrinolysis | | | |
|---|---|---|---|---|---|---|---|
| | | | | % lysis after 6 hours | | % lysis after 24 hours | |
| No. | Age (yr.) | Sample 2 | Sample 4 | Sample 2 | Sample 4 | Sample 2 | Sample 4 |
| 1 | 21 | 84 | 85 | .. | .. | .. | .. |
| 2 | 22 | 90 | 95 | .. | .. | .. | .. |
| 3 | 24 | 92 | 95 | .. | .. | .. | .. |
| 4 | 21 | 94 | 120 | .. | .. | .. | .. |
| 5 | 22 | 122 | 140 | .. | .. | .. | .. |
| 6 | 21 | 82 | 98 | .. | .. | .. | .. |
| 7 | 22 | 152 | 123 | .. | .. | .. | .. |
| 8 | 22 | 128 | 186 | 25·5 | 0 | 100 | 18·5 |
| 9 | 21 | 85 | 90 | 100 | 39·5 | 100 | 100 |
| 10 | 21 | 103 | 91 | 78 | 57 | 100 | 100 |
| 11 | 20 | 50 | 83 | 100 | 55 | 100 | 100 |
| 12 | 23 | 60 | 100 | 100 | 55 | 100 | 93·5 |
| 13 | 22 | 146 | 115 | 0 | 0 | 92 | 92 |
| 14 | 20 | 81 | 115 | 3·5 | 9 | 100 | 100 |
| 15 | 20 | 80 | 108 | 96 | 41 | 100 | 100 |
| 16 | 21 | 179 | 80 | 0 | 0 | 97 | 100 |
| 17 | 21 | 53 | 140 | 97 | 100 | 100 | 100 |
| Aver-age | 21·5 | 98·9 | 109·6 | 60 | 35·6 | 98·9 | 90·4 |

TABLE II—EFFECT OF LIPÆMIA ON FIBRINOLYTIC ACTIVITY IN THE BLOOD OF NORMAL MALES AGED 38–50

| | | Euglobulin lysis-time (min.) | | Plasma fibrinolysis | | | |
|---|---|---|---|---|---|---|---|
| | | | | % lysis after 6 hours | | % lysis after 24 hours | |
| No. | Age (yr.) | Sample 2 | Sample 4 | Sample 2 | Sample 4 | Sample 2 | Sample 4 |
| 18 | 38 | 171 | 168 | 0 | 0 | 94 | 83 |
| 19 | 42 | 110 | 130 | 0 | 0 | 83 | 44 |
| 20 | 38 | 99 | 80 | 10·5 | 0 | 100 | 100 |
| 21 | 38 | 71 | 78 | 36·5 | 18·5 | 100 | 100 |
| 22 | 50 | 102 | 121 | 6 | 8·5 | 100 | 100 |
| 23 | 45 | 163 | 130 | 1 | 22·5 | 100 | 100 |
| 24 | 45 | 133 | 138 | 0 | 13 | 100 | 100 |
| 25 | 49 | 103 | 85 | 12 | 14 | 100 | 85 |
| 26 | 38 | 74 | 75 | 0 | 4 | 100 | 100 |
| 27 | 45 | 74 | 68 | 0 | 0 | 100 | 100 |
| Aver-age | 42·8 | 110 | 107·3 | 12 | 8·0 | 97·7 | 91·2 |

The fibrinolytic activity was assessed by each of two methods in 10 pairs of samples from each age-group; a further 7 in the younger age-group were tested by the euglobulin method only.

Both methods were tried because we wanted to check the suitability of the more easily performed euglobulin lysis-time method for this type of work. In preparing the euglobulin fraction from the plasma some of the β-lipoprotein is lost (Buckell 1958), and Greig (1957) has shown that the removal of β-lipoprotein by fat solvents from plasma enhances fibrinolysis. It seemed therefore that the euglobulin lysis-time and other methods based on the use of isolated euglobulins (e.g., fibrin plates) would not show to the full any inhibitory effect produced by lipæmia. Our results fully support this supposition. In a few subjects fat had a small effect on fibrinolysis as measured by the euglobulin method, in so far as the morning increase of activity was less in the presence of lipæmia than on the control morning; but the inhibition was very slight and much less than was produced with the whole-plasma method.

With Bidwell's (1953) method, the average in each group for both the 6-hour and the 24-hour lysis was smaller for the midday samples after fat than for the midday controls. These figures suggest there is a definite inhibition of fibrinolysis after the ingestion of 50 g. of butter, but only the 6-hour lysis in the younger group is statistically significant.

In 14 out of the 20 tests there was an inhibition of fibrinolysis on the test morning as compared with the control. In these 14, the inhibitory effect was sufficient to overcome the normal morning rise. In 8 of them the midday sample was less active than the pre-fat specimen for the same morning; this happened in 5 of the younger group and 3 of the older group. In 6 others the increase of activity on the test morning was much smaller than on the control day. In 6 of the 20 subjects the fatty meal did not inhibit fibrinolysis. In 4 subjects, 2 from each age-group, the morning rise of activity was greater on the test day than on the control day, while in 1 of each group there was virtually no difference between the control and the the test days.

In this small series some of the differences in the response to a fatty meal may, of course, have arisen because the degree of lipæmia present 3 hours after the

fatty meal varied. Barritt (1956) has shown that, in a group of patients with coronary disease, the clearing of visible lipæmia after a fatty meal was delayed as compared with controls matched for sex and age; and it may be that fat absorption varies with age. Be that as it may, it is clear, both from our controls and from the responses on the test day, that not only is there considerable variation between the fibrinolytic activity of individuals, but that the older group shows less fibrinolytic activity and less amplitude of change than the younger group.

### Discussion

If, as suggested by Duguid (1946), an atheromatous plaque may arise by the incorporation into the arterial wall of a fibrin deposit, then the factors determining deposition and removal of small mural thrombi are important. Greig first showed that a fatty meal could inhibit fibrinolysis (Greig 1956, 1957, Greig and Runde 1957). Biezenski and Moore (1958) found a depression of fibrinolysis during normal human pregnancy, and thought this might result from the increase in lipæmia which accompanies pregnancy. The effect of fat feeding on fibrinolysis in animals has been investigated by Kwaan and McFadzean (1957), Foster Scott and Thomas (1957), and Gillman and Naidoo (1958).

Our figures show that the fibrinolytic activity of plasma as measured by an adaptation of Bidwell's method (Biggs and Macfarlane 1957) can be decreased by eating butter. This decrease was greater, reaching statistical significance, in the younger men. As the general level of fibrinolytic activity and the amount of diurnal variation were both greater in the younger men, it seems that the fibrinolytic system becomes less flexible with increasing age.

### Summary

In 14 out of 20 normal men fibrinolysis was decreased 3 hours after eating 50 g. of butter.

This depression of activity only reached statistical significance in the younger age-group.

The plasma-fibrinolytic system becomes less flexible with increasing age.

Euglobulin methods cannot be used to assess accurately the effect of fats on fibrinolysis.

Our thanks are due to the board of governors of Charing Cross Hospital for financial support; and to the volunteers from Barclays Bank (73, Strand, and Charing Cross branches), from the Civil Service Stores, and from the Medical School, who made the investigation possible.

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# Medical Societies

## ROYAL SOCIETY OF MEDICINE

### Mental Hospitals

THE Section of Psychiatry met on March 10, under the presidency of Dr. ELIOT SLATER, to debate the motion "That Most Mental Hospitals Meet the Needs neither of their Patients nor of the Communities Which They Serve".

Proposing the motion, Dr. JOSHUA BIERER said that the patient needed to benefit from the total knowledge of psychiatry, including recent research, to be understood and be given the feeling that he was understood, to be treated like a normal human being and given security and love, and to have the opportunity of retraining and readjustment to life. Dr. Bierer suggested a wide role for the psychiatric services in the community, including the provision of guidance to parents, worried adolescents, those about to be married, and others. He believed that, although a few mental hospitals did remarkably well, basic inadequacies in the system made it impossible for them to give the service needed by the patient and the community; he wondered, too, whether locking people up sometimes made matters worse through the vicious circle of disturbance, cruelty, and restraint. He praised the pioneer use of community and democratic methods; but the innate historical force against change was to be reckoned with, and our present advances could easily prove tenuous. Dr. Bierer emphasised that mental hospitals could not meet the needs of their patients because they were not given the facilities and money required. If one doctor had to look after 200–800 patients, what could he do? The mental health services in this country should be given 50% of the money allocated for health as at least 50% of all patients suffered from nervous or mental diseases.

Supporting the motion, Dr. ARTHUR POOL described the evolution over eight years of his service in Oldham; this was run largely on an outpatient basis but with beds in a general hospital. The need had arisen from congestion in the 3000-bed mental hospital nearby, and the service had the advantage of cheapness. It led to the lower chronicity-rate of about 2%, compared with the usual figure of 10%. An obvious advantage in domiciliary psychiatry was that the patient and his background could be more clearly related and understood. He believed that environment and emotion determined ill health far more than did heredity, and he wondered whether the effectiveness of many physical treatments depended essentially on the alterations in the attitudes of the staff towards the patient which such treatment brought about.

Opposing the motion, Dr. A. A. BAKER read into it a vote of censure on mental hospitals, which he resisted. Far from failing the community, most mental hospitals more than met minimal needs, even with their present enormous handicaps. Too many psychiatrists prided themselves on admitting either very few cases or very many. He wondered how often opposition to mental hospitals derived from psychological factors, and he regretted that deluded ex-patients were enabled to allege cruelties on mass media.

Echoing Dr. Baker's demand for the mental hospital as a "base" for psychiatric activities, Mr. KENNETH ROBINSON, M.P., said that such a view did not imply opposition to community or any other schemes, and in fact it had been the mental hospital that had fathered progress in this direction. It was dangerous, however, to assume that everything could be done in the community, for the more seriously ill people would always need hospital care. The strain on a family from indiscriminate home treatment could be very great, and keeping one patient out of hospital seemed absurd if it made several others ill. There was a danger, too, that too much emphasis on home care might nullify some of the changes in public attitude, and that mental hospitals might again be regarded as dark and dreadful places. Mr. Robinson said that if a censure were involved at all it was on the community; and he compared the average weekly cost of the mental patient (£6) with that in a general hospital (£26), while the cost per patient of medical attention was only 5*s*. as against £3 per week. If, as many agreed, our mental hospitals provided on the whole as good a service as any in the world, they could hardly be said to be failing. In apportioning the blame for past neglect, he agreed that lack of adequate funds from the Treasury and Ministry of Health were factors, but he suggested, too, that the medical profession itself was much at fault.

At the vote the motion was rejected by 24 votes to 22; but there was apparently some uncertainty about the meaning of the resolution, and a number of members abstained.

# Reviews of Books

## A Clinical Introduction to Heart Disease

CRIGHTON BRAMWELL, M.D., F.R.C.P., emeritus professor of cardiology, formerly professor of systematic medicine in the University of Manchester, and consulting physician to the Manchester Royal Infirmary. London: Oxford University Press. 1959. Pp. 229. 21*s*.

A BEAUTIFULLY written, clear, and concise book on cardiology has resulted from Professor Bramwell's lifetime of work in this subject. It is short and yet little of importance is omitted. Though written around the patient, his diagnosis and his anxieties, there is sufficient description of modern hæmodynamics to satisfy most practising physicians, though not perhaps the physiologically minded student. It will be particularly valuable for a general practitioner or general physician who has not been brought up in modern hæmodynamic cardiology.

## Surgical Treatment of Mitral Stenosis

HELGE BADEN, Rigshospitalet, Copenhagen. Copenhagen: Stone Nordiske Videnskabsboghandel. 1958. Pp. 263. Danish Kr. 20.

THIS monograph deals with the detailed analysis of 165 patients treated surgically in the University Hospital, Copenhagen, between January, 1950, and March, 1955. It also contains an exhaustive statistical review of published work on the surgical treatment of mitral stenosis and an outline of the prognosis in three series of cases treated before the days of valvotomy. The data are well presented and discussed. Preoperative and operative findings are described and compared with those of other workers. The value of diagnostic criteria is then examined and finally the results of the follow-up are correlated with preoperative and operative data. Danish experience is essentially similar to that in Britain. This comprehensive and factual study, impeccably translated, will be very useful to all who are responsible for advising or carrying out surgical treatment in patients with mitral stenosis.

## Methods for Research in Human Growth

S. M. GARN, PH.D., and Z. SHAMIR, M.D., M.P.H. Springfield, Ill.: Charles C. Thomas. Oxford: Blackwell Scientific Publications. 1958. Pp. 113. 34*s*.

THIS short book is well written and full of common sense. As the authors say: " it is intentionally modest. It is more of a guide to methods than a handbook of growth research. Any of the chapters could be expanded to book length ". There are chapters on planning a growth study, the pædiatric examination, the taking of anthropometric and röntgenometric measurements, and ways in which the development of teeth, skin, hair, muscle, fat, sexual maturation, and strength may be followed. In practically none of these are techniques of measuring discussed or critical evaluations of competing techniques attempted; but the book gives a clear idea of the sort of things people do in growth studies.

## Difficult Diagnosis

H. J. ROBERTS, M.D., physician to the Good Samaritan Hospital, Florida. Philadelphia and London: W. B. Saunders. 1958. Pp. 913. £6 13*s*.

THIS large book is divided into two parts. The first is called Groupings of Related Diseases Frequently Producing Puzzling Illness. It contains a list of causes: endocrinopathies, metabolic disorders, hepatic disease and jaundice, and so on down to group 17, cutaneous medicine, which includes an atlas of systematic dermadromes containing 99 illustrations, 14 of them in colour. Part I ends with 103 pages of references, 1417 of them in all. Part II is a Classification and Analysis of Useful Diagnostic Procedures. It contains fourteen sections, each with an exhaustive list of possible special investigations, starting with normal values and ending with " clinical clues " where conditions in which abnormal values may be found are briefly listed. Part II ends with 406 references, and is followed by a special and a general index.

**Surface and Radiological Anatomy** (4th ed. Cambridge: W. Heffer. 1958. Pp. 355. 50*s*.).—It is hard not to overpraise this well-known textbook by Prof. W. J. Hamilton and Dr. G. Simon, which now appears in a new and much improved edition. A few fresh illustrations have been added, but the chief changes are the replacement of many of the radiographs and some rearrangement of the text, both advantageous. This work will help a wide range of readers, from the graduate student of radiology to the medical student in the dissecting-room. Perhaps its most valuable application, however, is in the difficult period after the second professional examination, when the student is thirsting for " the real thing " on the wards. All too often he jettisons much of his knowledge of the structure of the body, laboriously acquired from the overloaded course in anatomy. This book will go far in encouraging him to amalgamate purely topographic study of the cadaver with the dynamic construction of the bodies of his patients. For this reason alone it is strongly recommended as a companion to the standard anatomical text during the course in anatomy. A return to it in the early years of ward work would also be profitable. Many qualified doctors are loud in their disclaimers of anatomical knowledge; in fact most of them retain much of what they earlier learned, but this becomes so united with other considerations of pathology, physical diagnosis, and surgical manœuvre that they cease to recognise it as anatomy. This is as it should be, and perhaps this process of absorption of formal anatomy of the descriptive sort into the clinical mind might be augmented by some small changes in our conventional methods of teaching. However this may be, *Radiological and Surface Anatomy* is a work which will do much to bridge the gap between formal anatomy and its chief application, diagnosis, and it will continue to receive the plaudits of many professional anatomists.

**Systemic Ophthalmology** (2nd ed. London: Butterworth. 1958. Pp. 711. 105*s*.).—A well-chosen team of writers is ably coordinated by Prof. Arnold Sorsby, the editor. The work is divided into six parts concerned with: (1) prenatal pathogenic influences; (2) inflammation, allergic reactions, and infections; (3) nutritional, metabolic, and endocrine disturbances; (4) central nervous system; (5) cardiovascular and hæmopoietic systems; and (6) other general disturbances caused by skin disorders, maternal and neonatal disorders, infections in the neighbourhood of the orbit, injuries, neoplastic metastases, and senescent changes in the eye. The whole work is admirably balanced, well written, and authoritative. This edition, like the first, will be of interest and value to ophthalmologists, neurologists, and physicians.

**Re-education of the Injured Shoulder** (Edinburgh: E. & S. Livingstone. 1958. Pp. 114. 12*s*. 6*d*.).—Mr. R. Barrie Brookes, F.C.S.P., has carefully surveyed reports on many abnormalities of the shoulder-joint. Half of the volume is appropriately concerned with degenerative disorders of the rotator cuff; while the remainder includes separate chapters on bursitis, bicipital tendonitis, and common fractures and dislocations. The anatomy of the region, and the way in which different lesions interfere with function, are by no means easy to describe; and, because of the author's clear exposition, this little book will interest orthopædic surgeons as well as physiotherapists.

**Selected Writings of John Hughlings Jackson** (London: Staples Press. 1959. Vol. I, pp. 500; vol. II, pp. 510. £6 6*s*. 2 vols.).—In 1931 the guarantors of *Brain* published two volumes of Hughlings Jackson's writings, the first devoted to papers on epilepsy and the second containing papers on evolution and dissolution of the nervous system, on speech, and on a wide range of other neurological topics. The writings were selected and edited by his old friend and collaborator, Dr. James Taylor. These volumes have been out of print for a number of years and have now been reprinted in the United States and published by the Staples Press. The new edition is an exact reproduction of the original one. Many of these papers are essential reading for anyone interested in neurology and psychiatry.

THE LANCET

LONDON 28 MARCH 1959

## Acute Otitis Media

THE Registrar-General reports that in 1957 [1] there were 187 deaths due to all forms of otitis media and mastoiditis, compared with 482 in 1949. Whether this satisfactory decline is due to decreased virulence of the infecting organisms, a lower overall incidence of otitis media, or the prevalence of antibiotic therapy is not known; but there is certainly no cause for satisfaction in the management of this condition. Survival with permanent injury to the middle ear and deafness is the modern criterion of failure. This problem, which was foreseen in the earliest days of the antibiotic era, and may have been aggravated by the prevalent neglect of surgical treatment, has still not received the study it deserves. ROSENWASSER and ADELMAN,[2] reporting cases of masked mastoiditis, found it " difficult to understand the almost dogmatic resistance of some experienced physicians to the fact that otitic complications are still occurring and require surgical intervention for their cure ".

The incidence of permanent loss of hearing is not accurately defined; and the effectiveness of present methods of preventing it is even more uncertain. Reports in which the follow-up assessment of hearing was based on non-standardised tests cannot be accepted, especially where young children are concerned. The Medical Research Council [3] found 68 cases of residual hearing loss about six months after the attack in a total of 1323 cases. No audiometry was done; and how many instances of deafness were undetected, especially in the large group (over 36%) under the age of 4, cannot be surmised. Very little has been published lately on follow-ups with audiometric assessment. DIXON [4] found that, of 88 cases, 4 had significant hearing loss on audiometry at an average of four and a half years after treatment. These patients were given penicillin, but in none was myringotomy thought necessary. No statistical conclusions should be drawn from this report, as DIXON himself made clear: the cases themselves were not representative, and the follow-up was highly selective.

Practice in the use of antibiotics is shown by the Medical Research Council's report to vary enormously with no apparent notable variation in the outcome—an odd situation that is likely to be explained only by adequate clinical research. FRY [5] believes that a majority of cases do not require antibiotics, having found them necessary in only 22% of 552 attacks. Others point out that antibiotic therapy is most effective when given early, and feel unable to distinguish in the early stages between cases in which recovery will take place without this treatment and those in which it will not. The only undisputed fact seems to be that when antibiotics are to be used they must be given by a reliable route in full dosage, and continued until a cure is obtained. The possible influence of antibiotic therapy in encouraging the emergence of resistant bacterial strains, and frustrating the development of natural immunity, should be seriously considered as a cause of recurring attacks. Both LUNDGREN [6] and POULSEN,[7] in studies with audiometry of cases treated before antibiotics were introduced, found that the risk of permanent deafness was much enhanced by repeated recurrence of attacks.

Myringotomy was undertaken only once in the Medical Research Council's series of 1323 cases, and not at all in FRY's series. Several workers [8-10] have expressed concern about the increasing number of cases of sterile middle-ear effusion following antibiotic treatment of acute otitis media. POPPER [8] refers to " antibiotic deafness ", and the term " glue ear " has been coined to emphasise the extreme viscosity of the fluid often found some weeks or months later at exploratory myringotomy. Whether this condition, if undiagnosed or untreated, ultimately resolves or leads to organisation and dense scar tissue is apparently not established; but the risk of scar formation seems real enough to warrant myringotomy in all cases not responding rapidly to antibiotics in the acute phase, and in those where deafness persists after the attack. Possibly antibiotics are being used too freely for this condition, and myringotomy too little. The discussions which have followed the Medical Research Council's report, and the contents of that report, have not helped greatly to solve these problems. The alarming lack of accurate knowledge calls for carefully planned investigations of acute otitis media by otologists and general practitioners working in unison.

## The Myelin Sheath

MUCH has been learnt in recent years about the structure, formation, and metabolism of the myelin sheath. From polarisation microscopy, electron microscopy, and X-ray diffraction analysis it has become apparent that the myelin sheath is far from being a simple tubular structure and in fact has a very distinctive internal architecture.[11 12] The sheath of every myelinated fibre is composed of many—often as many as a hundred—concentric laminæ or repeating units, comparable to the rings of a tree. Each lamina, which is less than a fiftieth of a micron in thickness, and thus far below the limits of resolution of the light microscope, is believed to be formed of two layers of protein molecules, arranged

1. The Registrar General's Statistical Review of England and Wales for the year 1955. H.M. Stationery Office, 1956. And personal communication.
2. Rosenwasser, H., Adelman, N. *Arch. Otol.* 1957, **65**, 225.
3. Medical Research Council. *Lancet*, 1957, ii, 510.
4. Dixon, J. W. *J. Laryng.* 1958, **32**, 227.
5. Fry, J. *Brit. med. J.* 1958, ii, 883.
6. Lundgren, N. *Acta otolaryng.* 1944, suppl. 53.
7. Poulsen, I. P. V. *ibid.* 1950, **38**, 120.
8. Popper, O. *S. Afr. med. J.* 1957, **31**, 54.
9. McKibben, B. J. *U.S. Armed Forces med. J.* 1958, **9**, 1425.
10. Pershky, A. H. *Amer. Practit.* 1957, **8**, 489.
11. Fernandez-Moran, H., Finean, J. B. *J. Biophys. biochem. Cytol.* 1957, **3**, 725.
12. Finean, J. B., Robertson, J. D. *Brit. med. Bull.* 1958, **14**, 267.

with their main axis lying circumferentially, bonded together by an intervening leaflet of radially oriented molecules of the myelin lipids. With the electron microscope each lamina is seen to form a complete ring—or possibly a fine spiral—of uniform thickness encircling the axon without any sign of break. How this laminated structure is laid down during the development of the immature animal is still not fully established.

Myelination in the peripheral nervous system (being simpler to investigate than in the central nervous system) was studied first; and this work led to the view that the laminæ were deposited spirally on the axon by the successive rotations round it of the enclosing Schwann cell—each turn being followed by the laying down of two additional protein-lipid repeating units.[13 14] Persuasive electron photomicrographs depicting this possible mode of myelinogenesis have been published; and, although the earlier supposition that the entire Schwann cell rotates now seems less likely, there are no obvious a-priori grounds for discarding the underlying concept that some film—derived from the cytoplasm of the Schwann cell and comparable to a pseudopodium—wraps itself round and round the axon, creating a further lamina at each of its turns.

The histological structure of the central nervous system differs substantially from that of peripheral nerves, and it is less easy to conceive of any comparable rotary mechanism in the myelination of its fibres. The belief, advanced many years ago by DEL RIO HORTEGA, that the oligodendrocytes participate in myelination in the central nervous system, in much the same way as the Schwann cells in peripheral nerves, has received much support; and comparative observations on local neuroglial proliferation and onset of myelination in different columns of the spinal cord of embryos[15] have added weight to this view. But, although the belief that these glial cells contribute in some unknown way to myelination is now widely accepted, failure to observe any wrapping process comparable to that described for peripheral nerves has led to the formulation of alternative hypotheses on sheath formation. LUSE, the first to employ electron microscopy for the study of myelination in the central nervous system, found the same multiple laminated structure in these sheaths, but was unable to detect any relation between the oligodendrocytes and the nerve-fibres comparable to that described for Schwann cells in peripheral nerves.[16] Myelinated fibres, she stated, " are rarely surrounded completely by the cytoplasma of a glial cell, and in this respect are different from peripheral fibres which are enveloped on all sides by the Schwann cells ". Nor was any wrapping by the oligodendrocytes seen by DE ROBERTIS et al.[17] in electron photomicrographs of immature mammalian spinal cords; they believe that the axons become surrounded and ultimately embedded within the cytoplasm of these glial cells and that the sheath develops as an envelope around the resulting " axon-oligodendrocytic membrane ". Thus, though electron microscopy has thrown some light on myelinogenesis in the central nervous system, much further work is needed before the process can be clearly pictured.

The success of PETERSON and MURRAY[18] in producing myelination in explanted embryonic spinal ganglia in tissue culture has opened new possibilities for following the process in living structures. Shortly after these findings were published, HILD[19] succeeded in cultivating and inducing myelination in explanted fragments of cerebellum, and so was able to follow for the first time the process with cells derived from the central nervous system. In some respects his findings fall into line with those of LUSE, for he observed no close association between the emigrant glial cells and sites of incipient myelination on outgrowing fibres. That these cells take some part in the process, however, perhaps by supplying the constituents of myelin, seem probable from observations by BORNSTEIN and MURRAY,[20] who found that in such explants myelination occurs only when the nerve-fibres and glial cells lie in the same vicinity. From these differing conclusions, it is evident that, while tissue cultures enable the process of myelination to be followed under especially favourable conditions, further experiments are needed to distinguish the respective contributions of glial cells and of axons.

Turning to biochemical studies on the metabolism of myelin, isotopic labelling of its constituents has rendered possible the determination of " turnover-rates " for the characteristic myelin lipids as for other tissue components. From some of the earlier of these investigations, notably those in which $^{32}P$ was used, it seemed possible that throughout life the phospholipid components of the myelin sheath were undergoing constant renovation. More recent work, in which $^{14}C$-labelled compounds have been employed, has thrown doubt on this concept of dynamic metabolism and replaced it by one of an essentially static nature. Professor PAYLING WRIGHT and his colleagues at Guy's Hospital have found from studies in the chicken[21] and (as they report in an article on p. 658 of this issue) in the rabbit that labelled cholesterol or serine, a precursor of other myelin lipids, injected into immature animals when myelination is taking place actively in their central nervous system, is deposited in the brain and spinal cord and remains there subsequently in scarcely diminishing amounts for many months. Presumably, these lipids are built into the laminæ, and once in place are outside the ordinary metabolic pool for such substances.

The general picture of the myelin sheath that has emerged in the past few years from these varied approaches is of a tissue element with a remarkably well-defined internal architecture, composed of mole-

13. Geren, B. B. *Exp. Cell. Res.* 1954, **7**, 558.
14. Robertson, J. D. *J. biophys. biochem. Cytol.* 1958, **4**, 349.
15. Bensted, J. P. M., Dobbing, J., Morgan, R. S., Reid, R. T. W., Payling Wright, G. *J. Embryol. exp. Morphol.* 1957, **5**, 428.
16. Luse, S. A. *J. biophys. biochem. Cytol.* 1956, **2**, 531.
17. de Robertis, E., Gerschenfeld, H. M., Wald, J. *ibid.* 1958, **4**, 651.
18. Peterson, E. R., Murray, M. R. *Amer. J. Anat.* 1955, **96**, 319.
19. Hild, W. *Z. Zellforsch.* 1957, **46**, 71.
20. Bornstein, M. B., Murray, M. R. *J. biophys. biochem. Cytol.* 1958, **4**, 499.
21. Davison, A. N., Dobbing, J., Morgan, R. S., Payling Wright, G. *J. Neurochem.* 1958, **3**, 89.

cular constituents which, once laid in place during developmental myelination, may remain in position with notable persistence, perhaps for the lifetime of the animal.

An expanding vista of research into the pathology of the demyelinating diseases is now opening for any investigator who is prepared and equipped to cultivate the newer experimental techniques. Perhaps the Ministry of Health, whose then Parliamentary Secretary, winding up a debate on multiple sclerosis, suggested that "it is lack of bright ideas and not of cash which is holding us back",[22] may be persuaded to reconsider its view.

## Nephrotic Syndrome

THE nephrotic syndrome, as we have lately remarked,[23] may arise from many different causes; and in any given case the cause may be difficult to establish. Protracted observation may make exact diagnosis possible, but often this is too late for treatment to be effective. New methods are urgently needed to give more information about function and structure, and about the effects of treatment.

JOEKES et al.[24] have made biopsies in 20 adults with heavy proteinuria and decreased plasma-albumin; of these 20, 16 also had increased plasma-cholesterol and generalised œdema. Sections 5μ thick were cut serially from biopsy specimens and stained with hæmatoxylin and eosin, and conventionally for fibrous tissue and amyloid. The results are of great interest. 8 cases are described as type-II nephritis,[25] 3 as benign nephrosclerosis, 2 as renal-vein thrombosis, 3 as focal glomerulonephritis, and 1 as probable systemic lupus erythematosus (S.L.E.); in a further 3 no lesion could be detected. In the United States KARK et al.[26] report similar studies in 98 cases. Of these, 46 were considered to represent some form of glomerulonephritis; a further 18 showed changes of S.L.E., and 15 of diabetes mellitus; lipoid nephrosis was diagnosed in 11 cases, amyloidosis in 3, and increased renal-vein pressure in 4, in 2 of which the renal veins were thrombosed; nephrosclerosis was found in only 1 case. It is noteworthy that pyelonephritis was not found as a primary cause in either series, although it was noted as a secondary lesion on 3 occasions by the American workers.

Thus the commonest cause of the nephrotic syndrome in both series was intrinsic renal disease—some form of glomerulonephritis. It may be doubted whether precision is added to the diagnosis by the term "Ellis type II"[27]; probably the descriptive terms used by the American workers are to be preferred. Moreover "lipoid nephrosis" is an unsatisfactory diagnosis,[23 28] as the American group admit elsewhere.[29] Leaving this aside, S.L.E. accounted for 18 (19%) of KARK et al.'s series, but only 1 (5%) possibly of the British cases. This discrepancy may perhaps be due to the smallness of the series. Diabetes mellitus is a common cause of the syndrome, but patients are likely to present with diabetes itself rather than nephritis.

JOEKES et al.[24] believe that in the 3 cases where they found no significant change in the glomeruli decreased tubular protein reabsorption may have been the cause.[30] An alternative explanation is suggested by the work of FOLLI et al.[29] who studied KARK's[26] 11 patients in whom lipoid nephrosis had previously been diagnosed. All of them responded excellently to corticotrophin or adrenal corticosteroid hormones, and after treatment all have so far remained well. In 7 cases the glomeruli were observed with the electron microscope. In all 7, striking and consistent abnormalities were found; these changes were limited to the epithelial cells of the glomerular tuft. The appearance of these highly specialised and delicate cells by electron microscopy has been well described in the normal[31]:

> They lie in Bowman's space, and are closely applied to the basement membrane. Their cytoplasm branches into large trabeculæ, from which numerous delicate foot processes (pedicels) arise. These processes extend to and cover the basement membrane, and are regularly distributed, being separated from each other by small spaces about 80Å wide.

In these cells the pedicels had been replaced by a continuous layer of cytoplasm of irregular thickness. Other but less striking changes were seen in the perinuclear cytoplasm. The changes, which are beautifully illustrated in FOLLI's[29] paper, are similar to those previously noted in children with nephrosis.[32 33] This work shows clearly that severe glomerular structural changes can occur which are invisible by conventional techniques but are easily detected by electron microscopy. Possibly the changes in the tubules result from consequent disturbance of glomerular function. FOLLI et al. describe a dramatic instance of this renal disorder:

> After the nephrotic syndrome had developed in a man of 19, renal biopsy revealed the epithelial lesion described above. A second biopsy was made after thirty-one days' treatment with prednisone, when the patient had lost all his œdema. Prednisone was continued; and a third biopsy was taken eight months after the onset of his illness, when he was clinically well. The epithelial cells were almost normal in the second specimen and were completely normal in the third.

FOLLI et al. offer no explanation for these observations. But it is highly probable that other cases of the nephrotic syndrome in which, when the kidney is examined by conventional techniques, the glomeruli appear normal and the tubules diseased may in fact be associated with similar changes. Here at last is a demonstration of at least one way in which treatment of the nephrotic syndrome[34] may produce benefit.

22. Vaughan-Morgan, J. K. *Hansard*, House of Commons, June 7, 1957.
23. *Lancet*, 1958, ii, 1000.
24. Joekes, A. M., Heptinstall, R. H., Porter, K. A. *Quart. J. Med.* 1958, **27**, 495.
25. Ellis, A. *Lancet*, 1942. i, 1, 34, 72.
26. Kark, R. M., Pirani, C. L., Pollak, V. E., Muehrcke, R. C., Blainey, J. D. *Ann. intern. Med.* 1958, **49**, 751.
27. See *Lancet*, 1956, ii, 663.
28. Allen, A. C. The Kidney: Medical and Surgical Diseases. London, 1951.
29. Folli, G., Pollak, V. E., Reid, R. T. W., Pirani, C. L., Kark, R. M. *Ann. intern. Med.* 1958, **49**, 775.
30. Freeman, T., Joekes, A. M. *Acta med. scand.* 1957, **157**, 43.
31. Hall, B. V., Roth, E., Johnson, V. *Anat. Rec.* 1953, **115**, 315. See Hall, B. V. *Amer. Heart J.* 1957, **54**, 1.
32. Piel, C., Williams, G. F. *J. Amer. med. Wom. Ass.* 1957, **12**, 273.
33. Farquhar, M. G., Vernier, R. L., Good, R. A. *Amer. J. Path.* 1957, **33**, 791.
34. *Lancet*, 1958, ii, 1219.

# Annotations

## THE WORTHING VERSION

THE progress of the Mental Health Bill through Parliament is lending urgency to the study of methods of looking after mental patients outside the hospital. Accounts of well-established prototypes at Nottingham and Amsterdam have several times appeared in our columns,[1] and a year ago Dr. Carse described[2] the district mental health service which he and his colleagues had introduced with success at Worthing. He has now carried the story further, and his report[3] to the South West Metropolitan Regional Hospital Board on the first two years of the scheme will encourage and inform those to whom the new Act will give responsibility for the development of community care.

Unlike the Nottingham and Amsterdam schemes, which are closely and formally associated with the health services of these cities, the Worthing version, though it has the good will of the local health authorities, is firmly based on a mental hospital—Graylingwell Hospital at Chichester. The intention is that, ignoring local-government boundaries, it will extend over the whole area which the hospital serves; but it is being introduced in three stages. Worthing and the surrounding district were chosen for the pilot scheme which was started in January, 1957; a service for Chichester and district began a year later; and with the start of the Horsham and Crawley service in the near future the whole catchment area of the hospital will be covered.

Under this scheme, a patient is referred to the service by his family doctor. A psychiatrist then visits him in his own home or (if the patient prefers) he is seen at the psychiatric outpatient clinic of the local hospital or at the day hospital of the service. Treatment is continued by further domiciliary visits and/or by physical or occupational therapy at the day hospital. (The active treatments offered include electroconvulsions, modified insulin therapy, psychotherapy, and drug abreaction.) A social worker attached to the service can help the patient and his relatives to deal with difficulties in his home or at work which may have been the cause of his breakdown. Laboratory investigations are undertaken by Graylingwell Hospital. Some patients, including those who need deep insulin-shock therapy, prolonged narcosis, or prefrontal leucotomy are admitted to the parent hospital from the service; but in practice it has been found that of every five patients four can be treated as outpatients.

The scheme was started in an attempt to halt the steadily growing number of admissions to Graylingwell Hospital and the consequent overcrowding of its wards. In this it has clearly succeeded. During 1958, when the Worthing and Chichester sections were between them covering some 70% of the hospital's catchment area, admissions to the hospital were 759 compared with 1345 in 1956 (the last year before the start of the scheme)—a reduction of about 44%. When the third section at Horsham and Crawley is in full swing it is confidently expected that there will be a further reduction. The population of the hospital has also fallen. Already there are 130 fewer patients in its wards and overcrowding has been overcome: indeed in some wards it has been possible to spread out the beds. This beneficent fall is partly due to the discharge of long-term patients; but here, too, the district service may have indirectly helped, for by reducing the number of admissions it has given the hard-pressed hospital staff more time for the reablement of these patients.

The many elderly people who live in the area had in the past inevitably added to the hospital's difficulties. The Worthing district service has reduced the number of admissions in the 65–75 age-group by slightly over half, and of those who are over 75 by slightly over a quarter. As these patients are often particularly reluctant to leave their homes, and as in hospital they tend to stay a long time, this is a valuable effect of the scheme.

So much for what may be called the service's negative work. Something of the scope of its positive work is shown by the following figures:

Last year the Worthing service treated 1253 cases, of which 1216 were new cases. Each day 30–40 patients visit the day hospital for special treatments, and no fewer than 554 domiciliary visits were paid to new patients alone. The younger Chichester service, in its first year, treated 925 patients. 365 first domiciliary visits were paid, and up to 30 patients received active treatments as outpatients each day.

As the service is an experiment in hospital administration, it is justifiable to examine its organisation closely. The figures which Dr. Carse offers seem to withstand critical scrutiny. The district services have reduced the number of hospital admissions without extra help, for they are manned by the permanent staff of the hospital. (Indeed, as Dr. Carse points out, it would be ironic if the salary of some senior members of the staff, such as the group secretary and the matron, should be reduced as a result of the success of a scheme which they have enthusiastically supported.) That the scheme has saved money as well as beds also seems clear. It is too early to see precisely what the effect of the fall in the hospital population may have on the annual budget of the hospital. But the 1957–58 figures show that the cost per hospital patient per week was £7 2*s*. 11*d*. During 1957 the total cost of the Worthing service was £18,291 (including the apportionment of salary of everyone who took part in the work, and the transport costs). On this basis the cost per patient per week was 9*s*.

Another important administrative point is the service's relation with the local health authority. From the beginning the authority's help and cooperation was sought and obtained. The medical officers of health of the area have taken a keen interest in the work, and the duly authorised officers and probation officers have given the service every help. But the service has been sponsored by the regional hospital board and administered by Graylingwell Hospital Management Committee; and for a service that provides treatment this pattern has (Dr. Carse thinks) much to commend it.

As he frankly admits, the service was started two years ago to try to deal with the hospital's problem of overcrowding. Today he would start it in the patient's interest. During thirty years' work in hospital he had, he believes, lost sight of the inevitable defects of institutional life and their effect on the patient.

" In the very early days of the Worthing Experiment ", he writes, " I learned somewhat to my consternation, that the man or woman I saw in hospital bore little resemblance to that same man or woman at home. At home, even though he was a sick man, he retained his identity and the sense of belonging: he was with his family and he felt secure because he was still in the community which he knew and which he understood. In hospital, the patient is an enforced member of a group living in an entirely artificial environment bearing no resemblance

1. Macmillan, D. *Lancet*, 1956, ii, 1094; Ling, T. M. *ibid.* 1954, i, 1127.
2. Carse, J., Panton, N. E., Watt, A. *ibid.* 1958, i, 39.
3. The Worthing Experiment, Jan. 1, 1957, to Dec. 31, 1958.

to anything approaching ordinary home life, but where everything is strange and often frightening. . . . I cannot believe that it is helpful in treatment for our patients to be compelled to live as a member of a large group of strangers all of whom are sick people, to be completely deprived of privacy and to have to submit to the segregation of the sexes."

Everyone who reads this humane and informative report will welcome the regional board's decision in the meantime to continue the Worthing experiment.

## ETHER ANALGESIA

INTEREST has been growing in the concept of general analgesia. Using ether, Artusio [1] described a plane in the lower border of Guedel's first stage where the patient is conscious and cooperative but free from pain; and he used it in over 100 major operations.[2] Klock [3 4] found a similar plane, which he calls "amnalgesia", in the first stage of nitrous-oxide anæsthesia; and Tom [5] used this plane for dental operations. A different approach to the same problem is that of Hayward-Butt [6]: in a high proportion of patients he produced a state of total analgesia by giving large doses of pethidine intramuscularly combined with pecazine ('Pacatal') and amiphenazole. He calls this state "ataralgesia".

A new apparatus designed by Nandrup [7] allows the administration of accurately measured low (0·1–7%) concentrations of ether (or other volatile anæsthetics, such as trichlorethylene and divinyl ether) carried in air. The non-rebreathing technique for which his apparatus is intended has several advantages: the concentration of the inhalation anæsthetic that reaches the patient can be accurately known (especially useful when ether is used for analgesia, since the limits of satisfactory concentration are narrow); and the patient's ventilation can be measured by the flow-rate of gases. The technique eliminates, moreover, the difficulties arising from the need to absorb carbon dioxide—inhalation of soda-lime dust, increased resistance, liberation of heat, and inadequate absorption of carbon dioxide.

The machine is based on an electromagnetic compressor which pumps air along two pathways. One stream passes through a needle-valve and flow-meter; the other, via another needle-valve, into a specially designed vaporiser where it becomes saturated with ether vapour. The air-ether mixture is then passed through another flow-meter calibrated to express the rate of flow in terms of pure anæsthetic vapour. The compressor draws a variable proportion of its air through the outer jacket of the vaporiser, thus enabling the temperature of the ether to be kept constant at 20°C.

An advantage of the apparatus is its easy portability, since no gas cylinders are required.

This apparatus has been used in over 600 administrations of analgesia both for major and minor operations. The concentration of ether required was not, usually, above 1·5%: this means that the oxygen of the inspired gas-mixture falls only 0·3%, a negligible amount. This concentration of ether is non-explosive.[8]

Something on the lines of this interesting apparatus will be essential for the measurement of ether concentrations if general ether analgesia comes into wide use. Whether this will happen, however, is doubtful. Results with nitrous oxide in non-hypoxic concentrations, even without analgesic supplements, are perfectly satisfactory in most hands,[9 10] especially when it is administered through a non-rebreathing apparatus (which allows the highest concentrations with safety [11]). Nor is the loss of consciousness at concentrations of 75% [12] necessarily a disadvantage; many, perhaps most, patients do not want to be awake during operations even if they suffer no pain. Since ether analgesia with Nandrup's apparatus requires no cylinders, it might have a useful place in field surgery, but among its disadvantages are that it is relatively complex, that it depends on electricity (though not necessarily on A.C. mains for it can be connected to a 12 V battery), and that it requires air at 20°C. Under normal conditions, though it may be too early to attempt a final verdict, non-hypoxic mixtures of nitrous oxide and oxygen, which are at least as free from toxicity as even low concentrations of ether, probably provide equally good analgesia.

## ORGANIC WASTES

A FEW years ago the engineer to the Dumfries County Council wrote an interesting and convincing description of the methods by which he converted organic wastes into useful fertiliser on a commercial scale.[13] His second book[14] repeats his lesson that much of the nitrogen, phosphorus, and water which reaches the sea via the sewers would be better used on the dry land for the benefit of agriculture and the ratepayer's pocket. Throughout the land untold miles of sewer stand as a memorial to the sanitary pioneers of the last century who freed us from cholera and enteric fever; and it is not only the enthusiasts for "organic farming" who are beginning to wonder whether the water closet is the last word. Every year we use more water, and use it more improvidently. Within living memory the objectors to any new scheme for water extraction were limited to a few anglers: at the moment the new proposals of the Torquay Corporation are opposed by the county council, competing local authorities, the river board, and amateur and professional fishermen.[15] It is fair to add that many local authorities on the coasts, having trapped the sewage, release it so near inshore that it is soon deposited on the beaches. It would seem foolish, too, that having discarded so much rich fæcal nitrogen we should have to replace it with what Mr. Jorrocks called "nitrate of sober"—except, of course, to the man spreading muck on a twenty-acre field on a wet December day.

Civilised man is a wasteful and extravagant creature, as anyone can see; but it could be argued that this improvidence is one of the rewards of civilisation: it is more pleasant to smoke cigarettes from the packet than fag-ends from the gutter. Moreover, it is open to argument whether we can yet relax our sanitary discipline. Every year about 200 cases of typhoid fever are notified, and each one is potentially the source of an epidemic. The Chinese are held up to us as model farmers by the "muck-and-magic" school; but they suffer dreadfully from intestinal infections of all sorts, almost certainly as the result of using human fæces as manure. It may well be true that "proper composting" destroys all pathogenic bacteria, but its advocates must convince those responsible for the public health of its safety not only in the back garden but when applied to the products of a large city.

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5. Tom, A. *Brit. med. J.* 1956, i, 1085.
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12. Gray, T. C. *Ann. R. Coll. Surg. Engl.* 1954, **15**, 402.
13. Fertility from Town Wastes. London, 1955.
14. The Wastes of Civilisation. By J. C. WYLIE. London: Faber & Faber. 1959. Pp. 160. 16*s*.
15. *Times* March 6, 1959.

We have built a system of sewage disposal which has freed us from serious risk of enteric fever. It is wasteful, especially of water, but to install any new system based on composting would cost a lot of money. No authority is likely to engage in this unless it is certain that there is no increased risk to health and that there is to be some reasonable financial gain. A few pages of detailed estimates are needed to convince the town clerk. The basic problem is to destroy the pathogenic bacteria in sewage and to reclaim the valuable elements and the water in which they are suspended. As a bactericidal process, heat must be rejected because of its cost, and chemical agents because we hope to make use of the sterile sewage as a fertiliser. To the best of our knowledge no-one has applied the modern knowledge of sterilisation by irradiation to organic wastes. If this were not too expensive it would remove one of the objections to composting, and we might be able to meet the organic school of thought halfway.

## INTUSSUSCEPTION

IN a recent review of experience at Johns Hopkins Hospital, Ravitch [1] discusses the management of 199 intussusceptions in children, and he refers particularly to 77 patients treated by barium enema. The clinical picture is only briefly described, and early diagnosis is so important that more detail would have been interesting. Morrison and Court,[2] in a survey of 100 cases treated in Newcastle, emphasised the usual finding of severe colic and pallor, with intervals of quietude, contrasting, for example, with the commoner picture of continual grizzling and flushing of the face in the baby with an upper respiratory infection. Most patients were feverish during the first day—another important observation, for anyone unfamiliar with the condition might take fever to mean an infection rather than intussusception.

The commendably few diagnostic errors in the Johns Hopkins series include an example of the dangerous confusion with dysentery. Pain with vomiting and a bloody stool can mislead, and in 1 case resulted in twenty-four hours' delay in treatment—a serious matter in this disease. Between 1939 and 1946, 40 cases of intussusception were treated, and in 5 an error in diagnosis delayed treatment and resulted in the death of the child. But no child has died of intussusception since 1946. From 1939 to 1948 the average duration of the illness before treatment was thirty-eight hours: since 1948 it has been only twenty-five hours. Ravitch attributes the improved results largely to the regular use of reduction by barium enema, and he remarks that Scandinavian and Australian reports have demonstrated that this is the safest method, though some surgeons would regard that as an overstatement. The method is undoubtedly valuable and does not seem to be associated with a high recurrence-rate. But series from Newcastle [3] and Boston,[4] for example, have shown excellent results with operative reduction. In Newcastle, Spence and Court [5] illustrated how a mortality of 14% was reduced to 4% by earlier treatment; and improved surgical management has now reduced this mortality almost to vanishing point.

Zachary [6] suggested that barium reduction was most likely to succeed in babies over six months of age and with a history of under twenty-four hours, and he proposed selecting such cases for its use. Many may prefer this approach to Ravitch's advice, which is to use barium first in all cases, and to persist for up to one hour if any progress is being made.

Perhaps the most valuable use of barium is in diagnosis. The tumour is often hard to feel through the cushion of wind in the overlying small bowel, and prompt X-ray examination, including barium enema, can avoid delay. The mortality of intussusception is negligible in the first twenty-four hours by either method of treatment, so the emphasis must be on investigation rather than observation. Spence pointed out that the general practitioner will see on average only 1 case every five years, so it is unreasonable to expect him to be expert in diagnosis. His responsibility is to suspect intussusception and refer the baby promptly for investigation.

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## TRIGEMINAL NEURALGIA

THE well-known triggering of pain in trigeminal neuralgia is often a useful diagnostic feature. In many cases a sensory stimulus applied within the trigeminal area will regularly precipitate an attack of tic douloureux. The trigger area varies from a small specific part, such as a particular area of the lip or of the gum, to the whole area of the second or third division of the nerve. The nature of the stimulus may also vary—a puff of cold wind, light touch to the affected area, talking, and eating and drinking are all well-known forms—but there is usually an element of light touch about it, strong or painful stimuli often having no effect. The threshold for effective stimulus varies; and patients themselves soon discover that during a bout of neuralgia triggering is all too easy, but that once the bout has subsided the stimulus may become ineffective unless prolonged and intensified.

Some attempt has been made to investigate in animals the mechanism of triggering by recording afferent potentials in the trigeminal nerve; but the problem has not been studied in man, if only because patients and doctors are loth to precipitate an attack of tic douloureux. Kugelberg and Lindblom,[1] however, have found some 50 patients stoical enough to have their pain deliberately precipitated, and to report on it.

Their work has confirmed and amplified clinical observation. Trigger zones, they find, are more commonly limited in area than large; and they are often constant for a given patient. As with other reflex phenomena, the trigger stimulus is subject to spatial and temporal summation and to a refractory period. Threshold for the trigger stimulus—apart from the refractory period—can be proved to vary. Kugelberg and Lindblom suggest that the majority of "spontaneous" attacks of tic may in fact be partially triggered. This would certainly account for the observed fact that a peripheral-nerve block, such as infraorbital or inferior dental, may dramatically terminate a given attack—a fact difficult to explain otherwise, since the evidence points mostly to a central lesion as the cause of the condition. The recognition of a refractory period might also have therapeutic value if patients and doctors can be found determined enough to exploit it.

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Dr. TOM HARE, professor of pathology at the Royal Veterinary College, London, from 1927 to 1933 and director of the Veterinary Research Laboratories from 1934 to 1940, died on March 17 at the age of 63.

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## Special Articles

# DEATH FROM TONSILLECTOMY

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"... except you utter by the tongue plain speech, how shall it be known what is said? For you shall be speaking into the air."—ST. PAUL (*I Corinthians*, XIV, 9, Douai Version).

THESE cases are to be found, by those who look, hanging in the cupboards beside the other skeletons of surgery. They are never brought out for an airing, nor does the slightest puff of air rattle the dry bones. They are unlikely to be found in the Registrar General's statistics, in the counterfoil stub of the book of death certificates, or even in the verdicts of H.M. coroners. A cloud of obfuscation maintains the illusion in the mind of the layman—and often of the doctor too—that the risks of tonsillectomy are negligible.

I shall describe four cases in which the patients died as a result of being put on the waiting-list for tonsillectomy (± adenoidectomy). (None of them occurred in the hospital where I have been working for the past three years.)

### The Cases

1. A boy, about 3 years old, was brought from the anæsthetic room and placed on the table for operation, already dead from ether anæsthesia.

2. A boy of about 7 had tonsils and adenoids removed during the afternoon. Although by the usual criteria his condition was satisfactory when he left the theatre, it was apparent by the early evening that the adenoid "bed" was still bleeding. After other expedients had been tried without success, it was decided, in the small hours of next morning, to insert a postnasal pack. The child was anæsthetised, with an open mask, on a trolley in a separate anæsthetic room, and then wheeled into the theatre. He was lifted from the trolley, audibly breathing, by a theatre porter and placed on the operating-table. His breathing stopped while he was being moved from trolley to table. An endotracheal tube was passed skilfully and speedily by the anæsthetist, followed by all customary routine; but the boy never breathed again.

3. A small boy, again about 3 (such a popular age for this operation), had tonsils and adenoids removed; and even before the end of the operating-list the surgeon was called to the ward because of the profuse bleeding. The child was at once taken back to the theatre where, under further general anæsthesia, bleeding points were ligated and silver nitrate was applied to oozing areas thought unsuitable for ligation. During the succeeding days the child was felt to be, on the whole, out of danger. A persistent clot in a tonsillar fossa caused no great concern, because the nurses had seen no fresh blood. But on the sixth day he was anæmic to an extent that could no longer be ignored, and half a pint of whole blood was transfused. Almost immediately afterwards he suddenly sat up in bed and then fell back, dead.

4. A woman of 33 had her tonsils removed under hæmorrhagic difficulties of such degree that the surgeon, on leaving the hospital, left a message about his precise whereabouts for the rest of the day. Although in the middle of the evening the patient was known to be bleeding, the house-officer did not notify the surgeon concerned. Later in the evening the woman was found dead in bed.

### Comment

#### FIRST CASE

I make no apology for ascribing this death to an operation that was never carried out. It would not have occurred had the patient not been selected for tonsillectomy.

The "cause" of death in this case was almost certainly psychological. It was the practice in this hospital to have twelve children on each "T. & A." operating-list. On this particular afternoon the child that died was number twelve. Should the anæsthetist concerned read this paper and recognise the case I think he will understand me when I suggest that death was due to the sheer boredom of anæsthetising a succession of twelve identical cases, and that the phenomenon is in no way different from industrial fatigue at the conveyor belt. If any anæsthetist reader is now feeling slighty sanctimonious, I should say to him "there but for the Grace of God ..." The remedy is the abandonment of sausage-machine surgery.

#### SECOND CASE

I attribute this death to two distinct though synergic factors. First, the decision to intervene—involving a second anæsthetic only a few hours after the first and after much blood loss—was ill judged. (Increasing experience makes one increasingly conservative in dealing with tonsillar hæmorrhage, though never forgetting how dangerous it can be.) Secondly, a mistake was made in allowing the child to be anæsthetised out of sight and sound of the surgeon and elsewhere than on the operating-table itself. The surgeon should observe all proceedings from the moment the patient is brought to the theatre, and be ready with suction, laryngoscope, and bronchoscope. His importance in these earlier stages is, of course, inversely proportional to the skill of his anæsthetist.

In the present case active respiration was audible when the child was brought from the anæsthetic room. Necropsy did not define the cause of death; but there was enough blood in the tracheobronchial tree to make it likely that the glottis had been suddenly obstructed either by fresh blood or by clot displaced from the nasopharynx. The distraught but efficient anæsthetist was unable to say whether there had been any such matter in the laryngeal region at the time of intubation. Predisposing greatly to displacement of clot was the inevitably somewhat rough handling of the boy in getting him from the trolley to the table.

The remedies, fortunately, are obvious.

#### THIRD CASE

This case differed from the first two in several respects but notably in the interval between operation and death.

Certain facts now to be mentioned throw light on the catastrophe. Perhaps the most material is that this child of 3 received half a pint of blood in less than half an hour. A total of half a pint of whole blood was intended, and the bottle was nearly empty when the child died after the time-interval stated. Why did this happen? Inadequate nursing staff is the answer. In this hospital the tonsil children were put at one end of a large ward otherwise occupied by general medical and surgical pædiatric cases. With the

best will in the world, the sister of such a ward is quite unable to exercise the necessary supervision over post-tonsillectomy cases in the hours after their return from the theatre, and when there is a shortage of staff it will be impossible to spare a nurse to watch a transfusion.

In my view, tonsillectomy cases should be housed only in wards devoted to otolaryngology, and staffed by nurses at least partly trained in its problems. If such facilities cannot be obtained, this type of surgery should not be undertaken. The potential benefits do not justify the risk of death.

In this case another factor was important. What had been regarded during life as a firm simple clot of a tonsillar fossa was found to extend nearly halfway down the œsophagus and was removed as a cast of the œsophagus. This finding raises several questions. How much credence should be attached to persistent nursing reports of "no fresh blood"? Should clots always be removed, no matter how firm they may seem? How much blood had this child lost as a result of oozing from the clot, over the back of the tongue, and down the œsophagus? Should complete investigation of the blood before tonsillectomy be mandatory in all cases?

In conclusion, then, why did this child die? From acute circulatory embarrassment consequent on too rapid transfusion of blood, for a degree of exsanguination far greater than was clinically suspected.

Once again, the remedies are obvious. But will they be adopted?

FOURTH CASE

I did not see this case, but the facts were reported to me by an eye-witness, and I record it because in many ways it is an extension of the principles enunciated under case 3.

The operation was performed in a small hospital which had no house-officer specifically accredited to the E.N.T. department. E.N.T. inpatients were attended, when this was thought necessary, by the houseman nominally appointed for general surgery, or by whoever chanced to be in the hospital at the time. None of these people had had any training in E.N.T. surgery.

In British hospitals, such a state of affairs is common; but I have almost given up hope that attention will be paid to it in circles of medical power, whether professional or lay.

**Discussion**

People who bear responsibility for unnecessary tonsillectomy—and therefore for its unnecessary disasters—include:

(1) The *consultant* whose judgment may be biased because the operation is an important source of private income.

(2) The *general practitioner* who knows little of laryngology yet condemns his patients to the operation en masse. Taking the line of least resistance, he does not even pause to consider whether perhaps his young patient snores because of allergic rhinitis rather than "adenoids". And the E.N.T. surgeon to whom he refers the child will probably not pause either. Tonsillectomy is preferred to ½% ephedrine nose drops.

(3) The *parent* who, before seeking medical advice, has decided that removal of tonsils and adenoids is the panacea for his child. The reason may amount to nothing more than an effort to keep up with the neighbours whose child was recently "done".

(4) The *medical officer of health* with a waiting-list of children from the school clinic and a committee which is determined to fight the battle of these poor "neglected" children.

(5) The *lay administrator*, who is perhaps the only unbiased observer of these events—but tends to think of waiting-lists as composed of numbers rather than people.

For my part, I am clear that the operation of "T's & A's" has such slender foundations and nebulous indications as to be quite unjustifiable when there is any chance of the kind of fatal accident described in this paper. If any reader does not agree will he say how many lives per annum can properly be expended in exchange for its supposed benefits?

If the true facts are not given to the public by the medical profession itself, may it not be the duty of the Minister of Health to present them, just as it is his duty to tell people about diphtheria, poliomyelitis, and smoking and lung cancer?

Objective handling of the situation by laryngologists, as a body, is unlikely so long as private practice continues, and particularly so long as patients seen in private consultation can be placed immediately, before their turn, in N.H.S. hospital beds. This practice, in recent years, has done more harm to the reputation of medicine in this country than any of the varieties of unprofessional conduct with which the General Medical Council chooses to concern itself. It is, of course, by no means confined to tonsillectomy; but this operation offers a major temptation to sacrifice the principles of surgery and common sense.

**Summary**

Four cases are described in which death was directly attributable to being placed on the waiting list for tonsillectomy.

The causes of such deaths are discussed candidly, and the ethical basis of this type of surgery is considered.

Many of the remedies are obvious but are too unpalatable for ready acceptance in the present atmosphere of surgical practice.

## PROPRIETARY PREPARATIONS

IN a report [1] published this week the Joint Committee on Classification of Proprietary Preparations (chairman, Lord Cohen of Birkenhead) recommends changes in the categories into which it classifies proprietary preparations for the information of doctors in the National Health Service. The former categories (1–6) were recommended by the Joint Committee on Prescribing. The present committee recommends a change from numbers to letters for identifying the categories, in order to avoid the mistaken belief that the numbers represented a descending order of therapeutic merit. The committee also recommends a new category of suspended judgment.

The revised categories now recommended for adoption are as follows:

*N.*—New drugs of proved value which are not yet "standard."

*S.*—(*a*) All preparations whose active therapeutic constituents are identical with or modifications of those of "standard" preparations (i.e., preparations described in the *British Pharmacopœia*, *British Pharmaceutical Codex*, and *British National Formulary*); (*b*) elegant preparations of drugs in category N; (*c*) mixture of drugs in category N with drugs in category S.

*P.*—Preparations which are not "standard" for which prima-facie evidence of therapeutic value is presented, but which the committee cannot accept as of proved therapeutic value without further evidence, which must be provided within a period stipulated by the committee.

1. Central Health Services Council and Scottish Health Services Council. Classification of Proprietary Preparations: report of the Standing Joint Committee. H.M. Stationery Office. 1959. Pp. 5. 6*d*.

*O.*—Preparations not " standard " which in the committee's view have not been proved of therapeutic value.

*H.*—Preparations which are a combination of drugs in category O with those in categories N, S, or P.

The committee suggests that preparations in categories N and P should be freely prescribable and those in S prescribable under certain conditions, and that practitioners should be discouraged from prescribing those in categories O and H. At the same time " there should be no absolute restriction on the prescribing by a general practitioner of any drug which in his opinion was necessary for the treatment of his patients ".

P is a new category of " suspended judgment " in which a new drug not yet standard, but for which there is prima-facie evidence of value, could be placed for a specified period during which the manufacturer would be asked to provide conclusive evidence of its value. At the end of this specified period (unless the committee otherwise determines) if the evidence is not presented the drug will be categorised as " not proved of therapeutic value ". During the period of " suspended judgment " the drug should be prescribable without the prescriber being called on to justify his prescription. For example, if it is claimed that drug *x* will arrest or cure cancer of the stomach even in a relatively few patients, and the prima-facie evidence presented with the claim is suggestive, the committee considers that it would clearly be wrong to withhold the drug until its value had been conclusively confirmed or refuted.

The report has been circulated to all practitioners, accompanied by a letter from Sir John Charles, chief medical officer, Ministry of Health, in which he says that " you will doubtless wish to refrain from prescribing any preparation in these categories (O and H) unless you are satisfied that it is essential for the treatment of an individual patient ".

## THE ROYAL COLLEGE OF PHYSICIANS

### A New Building

AGREEMENT has been reached between the Royal College of Physicians of London, the Canadian Government, and the Crown Estate Commissioners, whereby the college will surrender the lease of its site and building on the corner of Pall Mall East and Trafalgar Square in favour of the Government of Canada. This building will then become a part of the present Canada House. At the same time the Crown Estate Commissioners will grant to the college a lease of the site of Someries House in the south-east corner of Regent's Park, where a new college will be built. Mr. Denys Lasdun, F.R.I.B.A., has been appointed by the college as the architect for this building.

" . . . It appears that in any case major evolution has come to an end except in the one direction of better brains and minds, a direction pre-empted by man. . . . Pre-human evolution has come up against what we may call the biological barrier. Only man has been able to cross the barrier into the new psycho-social domain. Thus man is not only the most successful latest dominant type to date, the most advanced product of evolution, but the only type capable of achieving any important advance in time to come. What he does is decisive for the earth's vast future. He is the agent of the evolutionary process on this planet. This is so whether he knows it or not, whether he wants it or not: but he will do the job better if he does know it and does consciously want to do it."—Sir JULIAN HUXLEY in *The Destiny of Man* (London: Hodder Pocket Books. 1959. 2*s.* 6*d.*).

# Medical Education

## CONSUMER INTERESTS

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IN one of the papers in the final examination in medicine in Manchester University, the candidates have a choice of one out of six essay questions, the time allowed being three hours. Some of the subjects set have called for the arrangement of what should be familiar facts; and others have opened the door more widely to speculation. The general tendency of candidates has been to choose the " straightforward " type of subject. This makes it the more striking that in a recent examination just over a third of the candidates spurned such subjects as cardiac infarction, and steroid treatment, in order to discuss this subject—" Some practical ways in which medical education should be improved ". Perhaps I may now describe the answers, without committing myself to the proposition that medical education should be determined by what final-year students think of it.

Of the group of fourteen essays, two were judged to be outstandingly good, and four were very pedestrian. The students who chose to do this essay did not differ significantly from their colleagues in respect of failure-rate or general performance in other parts of the examination. The two students who did excellent essays were both in the upper sextile of candidates.

Following the arrangement of one of the better essays, it seems reasonable to outline the views expressed on education at school, in the preclinical and clinical years, and after qualification.

### BEFORE ENTRY

Only a few students considered the problems of school education and later selection for medical schools. They demanded, with differing emphasis, a broad general education, including languages; and a firm grounding in science. At one extreme was the student who extended a somewhat grudging permission to the schoolboy to do classics in the VIth form, on the grounds that " they will never be a loss to him "; at the other extreme the student who summarised his views in the metaphor, educationally still sound if perhaps architecturally outdated, that " A broad-based structure will stand higher and firmer than one with a narrow base ". Very recently, it has become the practice that almost all students should take their 1st M.B. examination externally; this change was welcomed even by those students who laid stress on the need for a broad school education.

Only three students discussed methods of selection. While all were critical, only one doubted the value of school reports, and another the value of examination results, which in his view could be attained " by dint of hard mental plodding ". The interview was criticised by two students, who both thought it should be replaced, or at least supplemented, by intelligence tests. One student thought that it would console anyone suffering from " temporary examination setbacks " to know that his " brain " was all right.

### PRECLINICAL SUBJECTS

The courses in anatomy and physiology escaped comment in only three essays; in the other eleven the

general tone was critical, although one student had appreciated the system of recurrent orals in anatomy as a mental discipline. The commonest complaint was that principles were lost in a mass of detail, and it was suggested that dissection could largely be demonstrated rather than performed; in this way the preclinical course could be shortened to one year, provided that revision of applied anatomy and physiology went on into the clinical period. The lack of apparent application to clinical problems was commented on by several students; two students commended warmly the practice of demonstrating suitable patients to students of physiology, but a third student condemned this on the ground that the students were not yet ripe for this experience. Some of the criticism was intemperately expressed in phrases such as " iniquitous ", and " crashingly boring ", as if an old sore had been reopened. Some concrete suggestions were made—that surface anatomy should be stressed, in view of its later application; that the broad topography of a part should be described before any detail was given; and even that medical students should be protected from excessive detail by sharing the course with students of nursing and physiotherapy!

### THE CLINICAL YEARS

As might be expected, most of the discussion was given to the clinical years. Several students suggested that teaching and examinations in pathology, bacteriology, and pharmacology should be completed in an extended preclinical period, so as to avoid distraction from ward work; another partial solution of the same problem was that the emphasis in pharmacology should be laid more on practical therapeutics, and the examination made part of the final. The commonest recommendation, made by all but one of the students, and by some very emphatically, was that opportunities for residence in or near the hospital should be much increased. This would allow the students to see more emergency work, to be given more responsibility for case-taking and practical procedures, and to enjoy a more definite footing in the wards. (There is at present a three-month period of non-resident clinical apprenticeship, which is much appreciated, and the essential recommendation is that this should be extended and made a resident appointment; several students suggested that this type of appointment should be extended to regional hospitals.) Some students wrote about the importance of the first clerkship in medicine, and the need for a thorough grounding in physical examination at this stage; but one student was heterodox enough to describe this as spoon-feeding, and another to suggest postponing instruction on physical signs until the student had had a number of patients demonstrated to him, " so that he knows something about diseases ".

Another majority opinion on the content of the course was that much more time should be given to " general practice ". In Manchester there is a scheme whereby a student accompanies a selected practitioner for two weeks; and this had clearly been a success with all the students who commented on it. One student wanted three months to be spent in this way, in defiance of logistics, if not of logic. Another student proclaimed that " the majority of students find their way into G.P. sooner or later "—whereas the relevant figures are of the order of 20,000 out of well over 80,000.

These two suggestions, of more residence and more experience of general practice during the clinical years, were both made by a majority of the students. Other points were made by one or two students only. The suggestions as to content of the course included more emphasis on mental disease; instruction on family planning, addiction, and homosexuality; some training in first aid; and guidance in " research " and the use of a library. On teaching methods, there were some criticisms both of lectures and of lecturers, and it was thought that attendance at all lectures should be voluntary; one student asked for more visual aids, and another for " gramophone records " of breath-sounds and cardiac murmurs. One or two students felt that the staff was inaccessible, and advocated a tutorial system. The two most revolutionary suggestions made were that all examinations except the final should be replaced by tutors' reports; and that the medical course should be arranged by " systems ", and not by subjects. This last suggestion probably derives from the Cleveland experiment, but it is interesting to find it made in a student's essay.

Three of the essays mentioned postgraduate education, advocating refresher courses, closer liaison between general practitioners and hospital doctors, and special revision articles in journals. Medical education of the lay public was discussed in three essays, all of which supported the use of television (" people will watch anything on television "). One view, rather unpractical, was that " radio and television education should be under the jurisdiction of a medical committee, as should medical articles in newspapers, books, and magazines ". The three students who discussed it all felt that education of the public in medical matters was important, and that the profession had a duty to improve it, because gossip and ignorance contributed to ill-health.

### "PRACTICAL MEDICINE"

Thus far I have tried to reflect as faithfully as possible the opinions expressed in this group of essays, and to withhold personal comment on these views. I have certainly no wish to compile an essay of my own on the same theme; but it is worth recalling that these essays were written as part of the final examination—i.e., at a time when the writers had been fully exposed to the rigours of the present curriculum, and before their spirits had been revived by the actual practice of medicine. It is not easy for a young man just emerging from the jungle to relate his recent studies to a coherent plan of medical education in which are fairly balanced the fruits of science, the accumulated knowledge from observation of human disease, and the techniques for applying medicine to the needs of the individual and the community; if he comments bitterly, or seems to lack perspective, whose is the fault?

In my view, the emphasis laid by most students on residence in hospital and on experience of general practice is a symptom of their desire to get to grips with " practical medicine ". I have no personal reservations about the value of longer residence and greater responsibility (under supervision) of the student in hospital, including regional hospitals; there are considerable practical difficulties, not the least of which is finding some time in which the student can escape from his organised commitments. I accept also the principle that the student should see something of general practice, but I would oppose any substantial extension of the period devoted to this. Apart from the many other claims on the student's time, my reasons for this cautious attitude are these. The aim of

the medical course, as I see it, is not to turn out one particular brand of doctor, but to help the student to equip himself for a profession which has many possible careers within it. On this view, the newly qualified student should have seen what general practice is like, but need not have carried out anything approaching " an apprenticeship in general practice ". Even if this were desirable, it would not be possible for any substantial proportion of students. An attachment for two weeks is something which can be (and has been) enjoyed by both practitioner and student; but a longer period could easily become a burden. A further very important consideration is that we have about 90 students each year, so that the three-month period suggested by one student would demand 22·5 years of practitioner-time annually. This seems to me far too great a burden to ask our colleagues in general practice to shoulder, even collectively.

In conclusion, I must thank my collaborators, too numerous to mention individually, who wrote the essays. The question quite obviously made them think; and I can now offer them in exchange the thoughts of an examiner on their essays.

## SCHOOL AND UNIVERSITY RELATIONSHIPS

MEDICAL education is unusual in that vocational as well as academic training must be given within the university. Some of the consequent problems were discussed at a conference held by the Leeds Institute of Education on March 14. The subject was School and University Relationships with particular reference to Medicine, and it was attended by grammar-school teachers and members of the Leeds faculty of medicine.

Prof. P. J. Moir, dean of the faculty, took the chair. Outlining the range of employment in medicine, he said that suitable candidates now have no difficulty in getting places in medical schools, and he thought there need be no fear of unemployment in the foreseeable future.

Professor Moir and Prof. Albert Hemingway, of the department of physiology, spoke of the growing concern in many medical schools (including Leeds) that students may be falling off both in number and quality. The increasing attractions offered by industry to graduates in pure science were one reason, they thought, why fewer first-class people now apply for entry to medical schools.

Professor Hemingway went on to say that medical students of the present generation tend to go up to the university asking to be taught rather than to learn, and they have a strong revulsion against the quantitative approach to problems. This is particularly discouraging at a time when the scientific foundation of medicine is becoming more and more important.

Reviewing the problems of selection for the profession of medicine, Mr. J. Dronsfield, headmaster of St. Peter's School, York, named as the three prerequisites for a medical training intelligence, interest in people and the ability to mix well, and a sense of vocation. Because widely different careers are open to the graduate in medicine, many feel that students should be drawn from the arts side as well as the science side of the schools, and some universities are willing theoretically to accept students on this basis.

At Leeds, students can take a 1st M.B. course at the university, but now that a fuller scientific background is essential for medicine, only the exceptional pupil who has taken an arts course in the sixth form is able to pass the 1st M.B. examination in the first year. Moreover, some local-education authorities are increasingly reluctant to give grants for 1st M.B. studies at a university.

# In England Now

*A Running Commentary by Peripatetic Correspondents*

WHEN our children all developed D and V and produced blood and pus, I thought there was something funny. So did my colleagues, who said that practically every child in the district had the same thing. Our children all recovered quickly, and as we were in the middle of the 'flu epidemic at the time we thought no more about it.

My son shares a desk at school with the son of one of the pundits at the local hospital. When his children were similarly afflicted, this great man was not satisfied with our rather casual approach. He took specimens to the lab. at his hospital. The bugs that were grown from them caused excitement in pathological circles. The public-health boys moved in. The affected children, by now as healthy as our own, were excluded from school pending two consecutive normal specimens. So were a number of other children who became caught up in the administrative machine.

That was a month ago, and the children are still running wild and harassing their parents. Rumour has it that no normal specimen has yet been received. Meanwhile the children of the more casual parents continue to attend school as usual. Feeling runs high. The conscientious parents say it isn't fair. The casual parents thank their lucky stars that they were casual, though in our heart of hearts we probably feel slightly guilty. Still, the holidays are approaching and then all the children will be running wild. By the time term starts again the whole sordid business will probably be forgotten.

* * *

By my reckoning Sir Clifford Allbutt must have been an octogenarian and not a septuagenarian when he was riding his tricycle through Cambridge in 1920 (*Lancet*, March 14, 1959, p. 574). Of such a venerable figure, stories were naturally few, but even that of how he had been seen going along Trumpington Street on the tricycle on the wrong side of the road with the red light in front was related with respect.

* * *

In a domestic crisis even a peripatetic correspondent is sometimes called on to make the bed. For the whole-timer this task is easy, but irksome; for the part-timer it is fraught with snags. Perhaps chief of these is the *retained hot-water bottle*.

This common condition is missed far too often, but with the possibility in mind, diagnosis is of course easy. If inspection fails to reveal a mass *before* pulling up the covers, then a typical succussion splash can usually be elicited by a sudden knee movement against the mattress. The cautious clinician may wish to confirm the diagnosis by fluctuation though this is not essential. Removal at this stage is simple and involves the minimum of tissue disturbance. Diagnosis *after* closure is completed renders treatment rather more difficult. For this stage there are three methods:

(i) The superior approach through the obvious planes of cleavage, which makes for rapid removal but necessitates almost complete remaking of the bed.

(ii) The lateral approach, which needs accurate localisation and a sound knowledge of the tissue planes, which are not easily found.

(iii) The inferior approach, which needs perhaps the most skilful siting and most intimate acquaintance with the anatomical relations in that area.

I personally favour the third approach, but would not recommend it to the occasional operator. It should be noted that, though separation in layers is essential at the beginning, closure can be completed in one layer with fairly satisfactory cosmetic results.

If these notes help to clarify a problem which, I suspect, is far commoner than we suppose, then I shall feel that my matutinal researches have not been fruitless. I have, however, now abandoned the investigation, because some thoughtful relation has given us an electric blanket.

* * *

It is said that when a Civil Servant reaches a certain stage of seniority he becomes entitled to a carpet in his office. The same stage in the progress of a consultant must be when he

has a white coat of his own, complete with buttons. First you must make it clear that you are past the stage of wearing a pus-covered frock coat. Then, if you are lucky, you may be given a tubular affair, which might fit one of the more sylph-like lady house-surgeons, stiffened like armour with the brand of starch used for the uniforms of matrons and home sisters, and with a row of linear holes on one side and stellate ones on the other. It is not easy to keep this presentable around one's middle during a ward round even with such devices as paper-clips and artery forceps. If, or when, I have a white coat of my own, complete with buttons, I shall be glad to come into hospital to do the registrar's emergencies for the fun of wearing it.

* * *

We all know that candidates for consultant posts have their troubles these days, but it was not till I sat on a selection committee that I realised that no other group of people are in such need of salvation from their friends.

One American referee allowed himself three closely typed pages of detailed and eloquent encomium, and the committee audibly relaxed when the end was at last reached. But there was an addendum which began " It is customary to give an account of the referee's qualifications . . ." A short biography of the distinguished professor followed. Another lengthy transatlantic report was redeemed by the last sentence: " Dr. Wilson married a lovely girl." We all felt rather sorry that Mrs. Wilson had not been summoned for interview.

There was nothing to choose between the four excellent candidates, and the committee finally settled for the man with the briefest testimonials.

* * *

We are all so clever at filling in forms nowadays that I wondered whether some of my fellow peripatetics might find my review form useful.

Professor ——'s masterly study of the — —— syndrome is timely indeed and few will dare not to add it to their shelves. The classification of the ——s has grown increasingly into a matter of urgency, the more especially since —— & —— showed that a large proportion of those cases in which the serum ——ase is markedly raised are in all respects clinically normal. Although the application of the methods described in chapters 7, 8, and 9 to human problems is not at once evident, the seven-figure tables concerning ——asia in the axolotl and in the Zambesi toadfish will undoubtedly come to be regarded as definitive. As Professor —— himself has said, " This work is authoritative ". It might be added with truth that it is also challenging; your reviewer could scarcely put it down, let alone pick it up.

The presentation is superb, the printing all but perfect (a full stop is missing from page 2081). Reading that must be considered indispensable to all candidates for higher degrees and to any who would wish to remain abreast of current developments in the field of the megalopathies.

* * *

ODE TO A NUCLEAR REMNANT

Ah, Karyorrhexis,* that forms for me
True nuclear fragments of the normoblast,
I see thy end-result, just two or three
Reddish-blue particles by phase-contrast.

Errant chromosomes? Can they derive
From mitotic spindle the similarity?
The true morphology shows they are alive,
Emphasised by Feulgen positivity.

Their home, their origin, anæmia,
Secondary, pernicious, post-splenectomy,
Acholuric jaundice, and leukæmia,
Tied with other signs of immaturity.

Ah, Karyorrhexis, that forms for me
Th' adorable, Howell-Jolly body!

* Karyorrhexis: breaking up of the chromatin of the nucleus into darkly staining granules (in necrosis of the cell). The author here seems to be trying to convey the impression that he knows more than in fact he does.

# Letters to the Editor

## CHILDREN IN HOSPITAL

SIR,—I hope you will not allow bickering over the exact meaning of inexact phrases to obscure the strangely irrational nature of the present attack on children's hospitals. Consider:

(1) As Lord Cohen puts it (March 14): " There is a compelling and urgent need for hospital accommodation in many fields." The Ministry's response to this need is to reduce permanently the beds available in the area concerned by 700—those in which the mental defectives of the Fountain Hospital now lie in squalor.

(2) The homeless defectives are then to be found room by turning out the 400 children in Queen Mary's into surrounding beds which are incontestably inferior in medical, surgical, nursing, educational, and welfare staffing and equipment. This means a certain number of avoidable deaths, not to mention crippling and unhappiness.

(3) The Ministry refuse to discuss their proposals; in particular to explain why they will not do the obvious thing and convert inefficient wards rather than efficient ones. If there is any reason other than that they are ashamed of their action and unwilling to expose their ignorance of what is happening to the children in their charge, I should like to know what it is. (Anyone who doubts their ignorance is recommended to read the report of the Acton Society Trust, 1959, on the Health Service considered from a business angle.)

(4) Lord Cohen says that cases whose treatment takes less than a month " could be dealt with satisfactorily in acute general hospitals with adequately equipped children's units ". He does not explain why a time-limit of four weeks makes diagnosis and treatment of babies and children so simple; but there is a catch about the " adequately equipped children's units ". As Lord Crook pointed out, they don't exist. There are some 300 beds labelled for children available; they are about 60% full. This means that over 250 children will have to go into urgently needed adult beds. (If the Ministry during their nine months' consideration have collected some accurate figures I shall be happy to accept correction.)

(5) As to the adequacy of these small, ill-equipped, and infrequently visited children's wards, the Platt report gives the startling information that 30% of the children in hospital are in adult beds, plus an unknown number in fever hospitals (though non-infective). Is there any explanation of this except that these wards are distrusted by parents, general practitioners, and the registrars who distribute cases? This might account for the letter of the local branch of the B.M.A. saying that if Queen Mary's is closed they will not be able to get their child patients " dealt with satisfactorily ".

(6) I find Lord Cohen difficult to understand. But when he pleads for a review of the situation and says " it may very well be as a result of that review that some hospitals which are now children's hospitals will, and should, be retained solely for the purpose of treating children ", does it not follow that the result may also very well be that the Ministry will suppress all of them? It is instructive but depressing to note that he does not even consider that we might follow the advice of the Royal College of Physicians and concentrate children rather than

scatter them; far less that we might compete with the work being done in the magnificent new children's hospitals of Canada, Australia, Sweden, and the U.S.A.

London, W.1. DENIS BROWNE.

## FATAL TUBERCULOSIS IN A GENERAL HOSPITAL

SIR,—Dr. Langford's letter of March 14 raises one of the most important problems in tuberculosis today in this country. For the past ten years or more, clinical workers have been greatly assisted by chest surgery and by specific drug therapy. Their patients have been found for them, at very considerable cost, by the mass radiography units, in relatively early stages of the disease. Yet it is tragically apparent that many advanced sputum-positive cases remain undiagnosed before death. It is these patients who, by infecting others, maintain the supply of younger patients to the sanatoria. The present Tuberculosis Regulations, by dividing the responsibility for prevention, largely contribute to this very unsatisfactory situation.

In cases diagnosed by postmortem examination, the diagnosis is included in the local registrar's weekly mortality returns to the local medical officer of health, and often this is the only way that health departments hear of such cases. Should the district in which the patient died not be a county borough, however, the local medical officer of health is not recognised by the Tuberculosis Regulations as the competent public-health field-worker for tracing the sources and the contacts. For some illogical reason, cases diagnosed after death are not notifiable to the Registrar General.

I understand there are, even today, areas where the county district medical officer of health is not informed of the results, if any, of source and contact tracing of cases within his district. In some areas, where such attempts at tracing are carried out, the work is left to a health visitor, who cannot have an overall knowledge of the local child and adult population.

Twenty years ago, source and contact tracing was often impossible, since most persons gave positive Mantoux readings, and facilities for chest X-rays were not readily available. Infected milk-supplies and mass subclinical infections in the child population confused the epidemiology, and some of our older chest physicians were, and still are, inclined to place little store on such fieldwork. Today, however, the epidemiological pattern is quite different; in most parts of the country one can assume that all children under 10 should be Mantoux-negative unless they have received an infection of human origin at home, at school, or when visiting or being visited by friends or relations. The Heaf gun has simplified mass-testing, and every child should be tested at the age of 2 and again at 5. At these ages the few positive reactors should make source-tracing relatively easy.

The Tuberculosis Regulations are ineffective today because they are based on an obsolete and outworn concept of the disease. They succeeded to a certain degree in the past, but they will not eliminate this present reservoir of infection. What is required now is a sense of real urgency whenever a new case is discovered. Each new case should be the subject of an investigation by a local tuberculosis team, and that team should include the family doctor, the district medical officer of health, the chest physician, and the health visitor. Wide contact-tracing should start immediately the case is confirmed, and failure to trace the source, in the case of younger patients, should be a matter of self-reproach to the team. Visits to the home, the place of employment, and the school should be made by the local medical officer of health personally (as he would in investigation into typhoid or smallpox cases), and should not be delegated to nursing staff. Contact-tracing often involves investigations into more remote contacts in other parts of the country, as when friends or relations who live elsewhere have infected, or have been infected by, the patient. By calling on other medical officers of health, I have in recent years traced the sources of three juvenile cases to an aunt in South Wales, an uncle in East Anglia, and to a grandfather in North London. In each case, the necessary clues were elicited only after second or third interrogations.

Tuberculosis in Britain will not be eradicated by regulations, but rather by an awakening of the consciences of all branches of the medical profession.

City of Chichester. D. WARREN BROWNE
Medical Officer of Health.

## GLUCOSE AND SUCROSE

SIR,—Your annotation of March 7 discusses the Food Standards Committee's Report on Soft Drinks.[1] You will perhaps allow a comment on behalf of the proprietors of a leading glucose beverage.

The committee takes the view that, for oral administration, neither dextrose nor liquid glucose has any physiological advantage over sucrose. This view is based on advice from the Committee on Medical and Nutritional Aspects of Food Policy, whose note on the subject is reproduced with the report. The note cites five papers as evidence that, given by mouth, sucrose can be metabolised a little more rapidly than dextrose. The reader may be surprised, therefore, to find that the first three are doubtfully applicable.

Both Higgins [2] and Deuel [3] found that the respiratory quotient rose more rapidly after taking sucrose than after taking dextrose. But, as Dodds et al.[4] point out, there was no evidence that the rise in the respiratory quotient after sucrose reflected carbohydrate utilisation in the peripheral tissues; indeed, both Higgins and Deuel themselves suggested that it could equally well be due to fat synthesis. The writers of the note say that " the issue " is the speed with which the energy of the various sugars is made available to the body. I suggest that the results of Higgins and Deuel provide no evidence of the relative speeds with which the energy of dextrose and sucrose is made available to the chief energy-requiring tissues —namely, muscle and brain.

Deuel et al.[5] compared the ketolytic effects of fructose, sucrose, and dextrose. A single dose was given to human subjects rendered ketotic by a 4-day fast and the resultant diminution in urinary ketones and nitrogen was measured over a period of 3 days. The authors concluded that " fructose and sucrose . . . exhibited a better effect on ketosis . . . than did glucose ", but add " although our data are insufficient to enable use to make a quantitative comparison ". But as the earliest urine samples analysed were the pooled samples for the 8 hours after the sugar was taken, the results cannot be expected to throw much light on the speed with which the sugars are ordinarily utilised.

As for the fourth paper (Cole [6]), it is only a review of earlier work. In the fifth, Rabinowitch [7] describes the effect of sucrose in hypoglycæmic diabetics. As he made no comparisons with dextrose, we are relieved of the

1. Ministry of Agriculture, Fisheries, and Food. Food Standards Committee: Report on Soft Drinks. H.M. Stationery Office. 1959.
2. Higgins, H. L. *Amer. J. Physiol.* 1916, **41**, 258.
3. Deuel, H. J., Jr. *J. biol. Chem.* 1927, **75**, 367.
4. Dodds, C., Fairweather, F. A., Miller, A. L., Rose, C. F. M. *Lancet*, March 7, 1959, p. 485.
5. Deuel, H. J., Jr., Gulick, M., Butts, J. S. *J. boil. Chem.* 1932, **98**, 333.
6. Cole, S. W. *Lancet*, 1935, i, 431.
7. Rabinowitch, I. M. *J. Nutr.* 1945, **29**, 99.

necessity of speculating how valid such comparisons would have been when applied to the non-diabetic subject.

Another curious discrepancy lies in the statement that hydrolysis of sucrose in the intestinal tissue "may form substances other than simple sugars which are more active in entry to metabolic cycles than are sugars themselves", citing Kiyasu and Chaikoff.[8] These workers found that, when fructose was absorbed from jejunal loops, "unidentified compounds" appeared in the portal plasma in addition to dextrose, fructose, and lactate. But the reader will search their paper in vain for any suggestion that these unidentified compounds were "more active": Kiyasu and Chaikoff make no reference to their metabolic significance.

On fructose the note says: "Fructose, which can be formed from sucrose by hydrolysis, is, unlike glucose, rapidly utilised in the body in a manner that is not dependent on the availability of insulin . . . and the evidence at present available suggests that fructose has an advantage over glucose in ease of utilisation by the body where there is a deficiency of insulin or a tendency towards such a deficiency". The relevance of this paragraph is not apparent. Some will derive the impression that a deficiency of insulin, or a tendency towards this, can occur in the non-diabetic subject, who may then utilise fructose more easily than dextrose. Is there a shred of evidence that such deficiencies occur in the normal—i.e., non-diabetic—subject?

It is not my intention here to deal with the relative merits of dextrose and sucrose. This will be done elsewhere. My purpose is to express our concern at the features of the note to which I draw attention.

Glucose Research Unit,
Beecham Group Ltd.,
Brentford, Middlesex. R. J. L. ALLEN.

SIR,—I am sure all clinicians will wish to protest against the Food Standards Committee's views on glucose beverages.

From many years' experience in the management of surgical cases, and in children especially, I should have said that the value of glucose preparations, when given by mouth in postoperative conditions and convalescence, was really beyond question. It is often important in these cases to supply calories in quantity and there is a weight of clinical opinion supporting the value and effectiveness of liquid glucose and dextrose for this purpose. Conversely, to give the same quantity of sucrose would be impossible as this would be so sweet and sickly as to be rejected by such patients.

As regards the utilisation of these sugars by the body, I think that the available evidence points clearly to dextrose, as such or formed from liquid glucose, as having the advantage. It can be utilised direct by all the body tissues, whereas sucrose must be transformed into dextrose before it is available as a source of energy to the peripheral tissues. I can see no practical or theoretical advantage in giving sucrose rather than glucose to a sick or convalescent person—in fact, the contrary.

Finally, with regard to nomenclature, I do not think that the Committee's recommendations are really well advised. The strange and unfamiliar terms which they propose in place of "liquid glucose" would, I should have thought, create confusion rather than remove it.

London, W.1. CECIL WAKELEY.

SIR,—I was interested to read your annotation of March 7. For some time I have felt that glucose drinks were of no particular value and might even have the disadvantage of causing loss of appetite in undernourished persons.

In the past few weeks, however, while treating elderly and frail people suffering from pneumonia, I have found that a glucose-containing drink seemed to be of value in that it was easily assimilated, whereas soup and food provoked vomiting and further fatigue.

Although loth to recommend a proprietary drink I feel justified in doing so for such cases.

Weybridge. P. B. SCHOFIELD.

## THE HAZARD OF WATER ENEMAS

SIR,—Water intoxication after the administration of water or soap and water as an enema is a danger which every doctor and nurse should heed. Your leader of March 14 mentions three known deaths following tap-water enemas; and I for one will never again give or order a hypotonic enema.

You suggested that those ordering enemas should see that "the amount of fluid given and returned is properly recorded". Flentic and Baptist [1] studied the water balance in patients given a 4-oz. (120 ml.) enema of hypertonic sodium biphosphate and sodium phosphate. After an average retention time of four minutes in 39 adults, the average volume of liquid expelled was 109 ml. (a slight decrease in volume, rather than the increase one might expect using a hypertonic solution). The sodium concentration in the expelled fluid was rather less than that in the enema solution.

These workers also found, in women constipated after delivery, that this phosphate enema produced a "good" or "fair bowel movement" in 84%, compared with 41% in patients given the same volume of distilled water or of isotonic electrolyte.

I now use a disposable 4-oz. phosphate enema (Harker's enema) and find it satisfactory, quick, and less disturbing to the patient than a conventional enema. It appears to be a safe device for use by the district nurse or by the intelligent mother of a constipated child.

Orpington, Kent. J. M. SIMISTER.

## SAFETY IN PROSTATECTOMY

SIR,—As a former member of the department of urology, University of Pécs, Hungary, let me challenge some of the statements made in this leading article last year.[2]

Amongst many hundred cases of prostatic obstruction I have never seen one which showed œdema without some additional complicating factor, such as cor pulmonale. On the other hand, I was able to demonstrate a reduction in the extracellular water from 18–22% to 12–15% body-weight (as measured by sucrose and inulin), while the patient's blood-volume was still maintained and the renal insufficiency was still relatively slight (total non-protein nitrogen 40–50 mg. per 100 ml.). These patients were neither vomiting nor overbreathing. Such findings suggest that water depletion is early and common in cases which are severe enough to lead to renal insufficiency. I certainly cannot accept your statement that the "dehydrated" appearance is usually due to uræmia rather than to water depletion. What common feature of uræmia could account for the dehydrated appearance other than dehydration itself?

Chronic urinary obstruction sooner or later leads to chronic pyelonephritis; and there must be some destruction of kidney substance even without infection. The ultimate damage (which may not amount to frank renal insufficiency) depends firstly on the degree of back-pressure, and secondly on the interstitial nephritis. We found increased loss of crystalloids such a constant and early feature of pyelonephritis that we came to regard it as characteristic.[3]

We also estimated the total circulating blood-volume and the albumin/globulin ratio in patients whose dehydration could not be relieved by intravenous fluids. In all of them we found the blood-volume decreased by 15–20% and an abnormal

8. Kiyasu, J. Y., Chaikoff, I. L. *J. biol. Chem.* 1957, **224**, 935.

1. Flentic, E. H., Baptist, V. H. *West. J. Surg. Obstet. Gynec.* 1957, **65**, 302.
2. *Lancet*, 1958, i, 947.
3. Horvath, C. S., Daviola, R., Kincses, J. *Z. Urol.* 1957, **50**, 120.

albumin/globulin ratio of just over 1. "Pushing" water by mouth (as mentioned in your article) and hypertonic and isotonic fluids intravenously were not only useless but actually aggravated the fluid and salt imbalance. In some of these cases, however, we succeeded in restoring the balance by giving a plasma-transfusion (5–10 ml. per kg. body-weight), followed by a slow drip of saline solution.

Our observations clearly showed that chronic urinary obstruction commonly leads to dehydration. The main cause of this is the inability of the damaged kidney to reabsorb crystalloids. A second cause is a change in plasma-proteins leading to altered plasma-osmotic pressure. It has been known for many years that no simple kidney-function test reflects true kidney function in cases of long-standing urinary obstruction. I think that careful study of the water and salt balance, as well as of the changes in blood-proteins and hæmoglobin level, is essential if prostatectomy is to be made safer.

Medical School,
Dunedin, New Zealand. C. H. G. HORVATH.

## HEADACHE OF MUSCULAR ORIGIN

SIR,—Of all the ill-defined diseases headache of muscular origin is perhaps the commonest, and one which occupies much of a general practitioner's surgery hours. I seek the courtesy of your columns to emphasise what was once well known before the army of drugs started its march—namely, the value of massage in treating this condition.

Often called fibrositic headache, its cause is either incoordination of the neuromuscular architecture of the head and neck, or fibrotic changes in the soft tissues; sometimes a psychological overlay is present, but this is not so much a cause as an aggravator. In the main, however, its ætiology is rarely clearly or wholly defined, and treatment often consists of "ringing the changes" with various salicylates or vitamin preparations.

While successful such treatment is symptomatic only, seldom of lasting value, and places a dependence on drugs which, when obtained apart from prescription, are commonly nostrums. My experience of over forty years has shown that reference of these patients to a physiotherapist versed in facial and cervical massage can result in a relief of greater satisfaction and permanency, and release the practitioner to treat headache of more serious import.

Leeds. AGNES RUDÉ.

## CHEMOTHERAPY OF BLOOD DISEASES

SIR,—In reviewing 25,000 cases of malignant blood disease I have found several areas of therapy which do not seem to have been explored within the past decade. Perhaps these apparent gaps may be due to my own failures in searching or to shortcomings in the index journals. I should be grateful for references to any clinical data on the following:

The treatment of polycythæmia vera with 6-MP, busulphan ('Myleran'), antibiotics, or corticotrophin/cortisone. (Only 1 case has been found of polycythæmia treated with folic-acid antagonists and colchicine.)

The control of chronic granulocytic leukæmia with folic-acid antagonists, antibiotics, or corticotrophin/cortisone. (Myleran therapy of mycosis fungoides and urethane therapy of reticulum-cell sarcoma also appear to be untried, and only 1 case of the latter disease seems to have been treated with folic-acid antagonists.)

In the present empirical state of the chemotherapeutic management of malignant blood diseases it would be significant to know if these possible methods of treatment have in fact been tried.

Furman University,
Greenville, South Carolina. JOHN R. SAMPEY.

## SPRAY-PACK THERAPY IN DERMATOLOGY

SIR,—Recently hydrocortisone has been marketed in the form of sprays. The earliest of these contained isopropanol as the diluent, with a propellant; but the intense stinging evoked when the spray was used on broken skin limited its use. A spray [1] has now been developed which does not contain isopropanol, and this can be used without stinging the patient.

This method of topical therapy is economical. Not only is a fine and even dispersal of the active ingredient obtained, so that as much as eight square yards of skin can be effectively covered by 100 ml. of lotion, but the efficacy is greatly enhanced by virtue of the volatility of the medium. Hydrocortisone in a dilution of 1/1000 in a volatile medium seems as good as 1/100, where the medium is non-volatile and remains on the skin.

The principal benefit of this method of therapy is seen in the acute and exudative phases of eczema and dermatitis, particularly where large areas are involved. Application is both clean and easy, and results in much time being saved where nursing staff are carrying out treatments.

Northampton. I. S. HODGSON-JONES.

## REINSTATEMENT AFTER WRONGFUL DISMISSAL

SIR,—I read with concern in your issue of March 14 of the discussion in the House of Lords on the wrongful dismissal of a consultant. The Earl of Onslow made statements which, I feel, it is only proper I should correct.

The Earl stated that this was a takeover case from the voluntary hospital to the National Health Service. The consultant was employed at the Boundary Park General Hospital which was administered by the Oldham County Borough Council, and at no time has it been a voluntary hospital.

The Earl also said: "I understand that he has a large private practice." The source of this information is not disclosed. It is certainly not contained in the judgment because Mr. Justice Barry states "that the Plaintiff's private practice fell off quite substantially after his employment at the Boundary Park Hospital had terminated". Through his wrongful dismissal this consultant is excluded from all private beds in the Hospital Service and there are no nursing-homes in the district. It is correct that he is employed by a local authority. The consultant was on the "appointed day" the consultant obstetrician (part-time) to the Oldham local health authority and his appointment has never been terminated by the council, as the council were satisfied that his appeal should have been heard.

The Earl of Onslow also said: "I understand that this doctor has received substantial tax-free damages, as awarded by the Judge, who at the time said that there was no possibility of reinstatement." Mr. Justice Barry made no mention of reinstatement in his judgment, but he did make a declaration against the Minister that he acted wrongfully and in breach of his statutory duty. The damages paid are described as substantial and tax-free. They were based on the loss of salary for five years together with £1500 for loss of private practice over this period. The hearing was in December, 1957, eight months after the five-year period of loss of earnings. Two years have now almost passed and the consultant has no hospital appointment. In view of recent decisions Mr. Justice Barry had to take income-tax into account, otherwise the damages would have been nearly £15,000. Nor was the consultant at the time of his dismissal in a post which the hospital board chose to divide into two. An additional post was created some six months before this and an additional consultant appointed before he was dismissed. None of the advocates for justice to be done in this case have ever suggested that either of the two consultants now employed should suffer any loss of sessions. This would be creating further injustice.

The Earl finally says "and he is earning a good living in his own profession". This cannot be the case since the only appointment the consultant holds is with the Oldham County

1. 'Cortril', Pfizer.

Borough Council and his remuneration has averaged less than that for four sessions per week on the Whitley Council scale for part-time consultants employed by local authorities.

These serious official errors continue to illustrate the grave injustice that has been done in this case. I would add that during the hearing the Judge stressed the fact that the officials of the Oldham Corporation and the consultant were in no way to blame for the administrative errors.

Public Health Department, Oldham. J. T. CHALMERS KEDDIE Medical Officer of Health.

## A CLINICAL THERMOMETER'S VAGARY

SIR,—I have had an unusual experience with a clinical thermometer which should be reported in order to prevent others being caught in the same way. As I removed the thermometer from a patient's mouth, I saw the mercury column flashing back to stop at 97·2°F. Subsequent checking with a different instrument showed a temperature of 100°F.

I have hitherto regarded clinical thermometers as either broken or functional, and, looking back over the month that I have owned this instrument, I believe that it has misled me very seriously over a patient with appendicitis, and in sundry other lesser matters. It would seem that it is advisable to do an acceptance check on the reliability of the constriction in the mercury column before putting clinical thermometers into use.

Monmouth. J. L. INSLEY.

## TREATMENT OF FRACTURED NECK OF FEMUR

SIR,—Mr. Murley (Jan. 3) has made some useful and interesting observations on this subject. His suggestion that early weightbearing does not appear to jeopardise the chances of union in the majority of cases is borne out by a review of cases similarly treated in this hospital.

For the past ten years, the intracapsular fracture has been pinned more or less as an emergency. Some have been bad surgical risks, but even these do better if pinned today rather than wait for the physician's assessment of tomorrow. Most are already up in a chair before the wound has healed, and are about the ward on crutches within three weeks. The elderly cannot use crutches without some weightbearing on the affected leg, so that most have been weightbearing during the early convalescent period.

We are taught that weightbearing is to be avoided until union is established, but the assessment of radiological union is a difficult matter, and it seems better to accept a painless hip with no change in the angle of the fracture as being a fair indication of bony stability.

If mechanical fixation is unsound, early weightbearing brings the matter to a head and this seems preferable, since it is better to have a positive answer to a doubtful pinning in the early convalescent phase than to expect that prolonged bed rest will produce a satisfactory result. In the series of some 170 consecutive cases reviewed in this hospital, the fracture either gives way early because of poor mechanical fixation, or at some time later as a result of necrosis. The incidence of necrosis appears no higher than that encountered by other authors, so weightbearing does not seem to have any direct influence on this complication.

The use of the word " emergency " is not intended to mean midnight pinnings, or that the poor-risk should be committed to surgery without assessment. It is felt, however, that the fractured neck in the elderly is better pinned before the next routine slate, and the bad risk becomes a reasonable one as soon as the fracture is secured and convalescence started.

Addington Hospital, Durban. JOCELYN HILL.

## MEPROBAMATE AND THE CARDIOVASCULAR SYSTEM

SIR,—Side-effects apparently associated with meprobamate seem worth recording since the drug is widely used today.

A housewife of 44 was admitted to this hospital on June 6, 1958, because of a sudden intense maculopapular rash which had appeared shortly after an initial dose of meprobamate (400 mg.). It involved the arms, chest, lower abdomen, and groins. Temperature 101·1°F (38·4°C). She had headache, dizziness, palpitation, weakness, nausea, and pain in the chest and arms. The only abnormal laboratory finding was leucocytosis (14,000 per c.mm.).

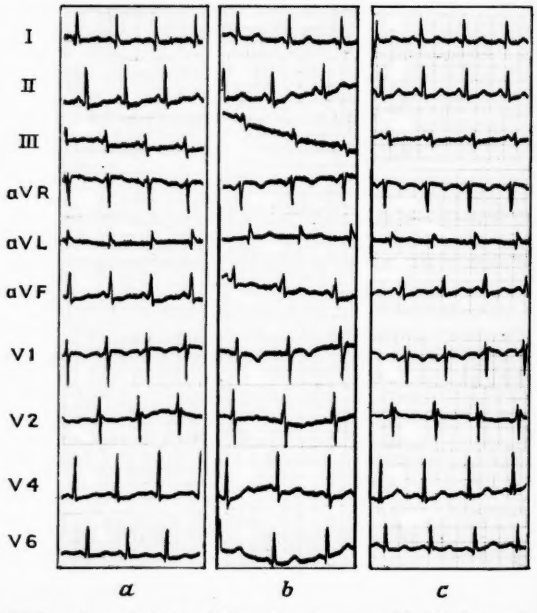
The electrocardiogram (E.C.G.) showed diffuse myocardial damage, evidenced by moderately depressed T waves throughout the tracing (fig. *a*). The second E.C.G. on the fourth day in hospital was essentially normal; a similar tracing a week later was also normal (figs. *b* and *c*). Recovery was uneventful and rapid. Fever declined on the third day. Physical examination of the heart revealed no significant changes apart from slightly weaker sounds than normal and tachycardia. Blood-pressure on the first day in hospital was 100/60 mm. Hg; slightly lower than readings taken before the episode. The symptoms cleared completely in a few days after treatment with anti-histamines.

The coincidence of a widespread rash, and an abnormal E.C.G., and their simultaneous disappearance, is likely to be significant. The case accords well with a description of skin rash after a first dose of meprobamate.[1]

Severe hypotension due to meprobamate was an alarming feature in one series.[2] Hypotension, vomiting, diarrhœa, strabismus, and anuria were reported by Riising (quoted by Adlin et al.[3]).

In a fatal case [3] there was high fever, itching, burning of the eyes, generalised erythematous rash, vomiting, hypotension, and swelling of several interphalangeal joints of the fingers. The E.C.G. was consistent with " diffuse myocardial abnormality associated with sinus tachycardia ". Terminally the patient had oliguria and uræmia. At necropsy the main finding was

1. Friedman, H. T., Marmelzat, W. L. *J. Amer. med. Ass.* 1956, **162**, 628.
2. Scott, P. A., Grimshaw, L., Malony, H. M. *Arch. intern. Med.* 1957, **100**, 484.
3. Adlin, E. V., Sher, P. B., Berk, N. G. *ibid.* 1958, **102**, 484.




**E.C.G.s (a) on admission, (b) four days later, and (c) a further week later.**

left ventricular hypertrophy (1·8 cm. in thickness). The coronary arteries showed minimal atherosclerosis, but the vessels were patent. There was an accumulation of large eosiniphil-staining cells with eccentric nuclei at the base of the tricuspid valve. A small proliferative lesion, of small lymphocytes and larger mononuclear cells, was found at the base of the aortic valve.

Reports of side-effects of meprobamate say little about cardiovascular lesions. Adlin et al.[3] give valuable details of the myocardial involvement which could be predicted ante mortem from the E.C.G. changes.

Bernstein and Klotz [4] quote Collin's observation of a patient with angioneurotic œdema, fever, erythema, and an irregular rapid pulse. The E.C.G. showed small complexes with a flutter-fibrillation rhythm, and ectopic ventricular beats.

Final evaluation of the abnormal E.C.G. in our patient is difficult. To infer transient myocardial damage reflected in the E.C.G. seems unwarranted without histological corroboration. Further study of the effects of meprobamate on the cardiovascular system seems to be needed.

Department of Internal Diseases,
Hasharon Hospital,
Petah Tikwah, Israel. J. SHAPIRA.

## MENTAL HEALTH BILL

SIR,—The recent correspondence on mental-hospital administration has thrown light in dark places; it is surprising that only the advent of the Mental Health Bill started a discussion some ten years overdue. There is one point on which I am not clear. Do any of those correspondents who advocate the retention of medical superintendents believe that they should still retain the right to interfere with other consultants' patients as was their wont? Contrary to what Dr. Bickford implies in his letter of March 14, I can assure him there are still mental hospitals in which consultants are not permitted either to write reports to the Board of Control or sign the death certificates of their own patients. If these petty and obsolete powers are to persist it is unlikely we shall see the rise in status of consultant psychiatrists for which Dr. Oldham (March 14) hopes. Few doctors of any stature will enter a specialty where they can never have full charge of their own patients.

That there should be one consultant to speak for his medical colleagues is a more tenable proposition; for a hospital can no more govern itself than an army can lead itself. That this consultant should hold office for a period sufficient to ensure continuity of policy is, as Dr. Bickford points out, also desirable. This could be achieved by appointing a medical superintendent for five years, extendable once for a like period. Surely most men can accomplish any worthwhile policy they possess in this time. If their policy is not worth while it would provide opportunity of painless replacement without waiting (as may happen now) for quarter of a century. Or is it seriously maintained that a medical superintendent appointed, say, at forty, retains all his vigour and freshness of outlook at sixty?

Finally, I was interested to read there was a "philosophy of medical administration", even though Dr. Bickford found it hard to describe. Is there a philosophy of occupational therapy, dietetics, and nursing as well?

Littlemore Hospital, Oxford. J. E. DUFFIELD.

SIR,—If the responsibilities of consultant psychiatrists are brought into line with those of consultants in other specialties a big step would be taken toward making the job—apart from the money—worth having.

It would mean the psychiatrist in future would be able to have the clinical independence essential in his work. This would in turn, I believe, attract many more young doctors of the right calibre toward a specialty which at the moment urgently needs a blood-transfusion.

Taunton. M. F. BETHELL.

## IS PEPTIC ULCER AN ENDOCRINE DISEASE?

SIR,—"Medicine seems to be becoming too difficult", comments your leading article of Jan. 17. May I make it even more so by presenting the following case?:

A 68-year-old gardener was admitted to the Manchester Northern Hospital on June 21, 1953, several hours after suddenly developing severe abdominal pain and vomiting. For 22 years he had suffered from diabetes mellitus, and latterly he had kept his urine sugar-free with 22 units protamine-zinc insulin daily. There was no history of peptic ulceration.

He was an obese elderly man, and showed furring of the tongue and slight "guarding" with tenderness in the right subcostal region. No other abdominal signs were discovered. His temperature was 99·8 F, his pulse-rate 88, his blood-pressure 130/90 mm. Hg. The urine contained sugar+++ with a trace of acetone. Insulin was given but he died after 24 hours.

Postmortem examination 8 hours later showed generalised peritonitis due to perforation of a chronic ulcer in the first part of the duodenum. The pancreas looked normal. Microscopy confirmed the benign nature of the ulcer. Areas of the myocardium were fibrosed from old infarctions. Both kidneys showed the features of healed pyelonephritis with no evidence of diabetic glomerulosclerosis. Blocks from the head and tail of the pancreas appeared normal. None of the islets were fibrosed or hyalinised; but in one section an islet-cell adenoma was found, composed of irregular cords of cells with a pale cytoplasm. Unsuccessful attempts were made to stain differentially the islet-cells using Gomori's chrome-alum-hæmatoxylin-phloxine method.

The Zollinger-Ellison syndrome was unknown to me then, but the combination of peptic ulceration, diabetes mellitus, and an islet-cell adenoma struck me as odd. A review of the literature showed that islet-cell adenomas—most of them microscopic and inactive—were an incidental finding in about 6% of postmortems, but in diabetics they were much more infrequent; thus Warren and LeCompte [1] encountered 3 in 811 diabetics and found reports of 3 more. I thought that Ogilvie's [2] demonstration of enlarged islets in obese persons, which he ascribed to a pituitary pancreatrophic factor, might explain the association of the adenoma and the diabetes, especially if the latter were of other than insular origin.

Peptic ulcer with diabetes mellitus was unusual.[3] Marble [4] suggested that differences in age and the duration of life in the two diseases could explain this. (About three-quarters of the diabetics in the United States were over 50, whereas peptic ulcer was more prevalent in younger people.) Was the development of peptic ulcer in my patient fortuitous? Muir [5] had demonstrated that acid secretion was stimulated by insulin, particularly in patients with duodenal ulcer, where it also shortened the gastric emptying-time. Cunningham et al.[6] reported a case in which hyperinsulinism due to multiple islet-cell tumours was associated with a duodenal ulcer and hyperplasia of the adrenals. They suggested that hypoglycæmia had enhanced a pre-existing hyperchlorhydria. I thought

4. Bernstein, C., Klotz, S. D. *J. Amer. med. Ass.* 1957, **163**, 930.

1. Warren, S., LeCompte, P. M. Pathology of Diabetes Mellitus; pp. 51. 53, 241. Philadelphia, 1952.
2. Ogilvie, R. F. *Edinb. med. J.* 1944, **51**, 460.
3. Bockus, H. L. Gastroenterology; vol. 1, p. 324. Philadelphia, 1944.
4. Marble, A. *in* Treatment of Diabetes Mellitus (edited by E. P. Joslin et al.); p. 454. London, 1952.
5. Muir, A. *Quart. J. Med.* 1949, **18**, 235.
6. Cunningham, L., Howe, P., Evans, R. W. *Brit. J. Surg.* 1952, **39**, 319.

it likely that the hypoglycæmic action of insulin accounted for my patient's ulcer.

Since then a strong possibility has arisen that there is a second pancreatic hormone—a hyperglycæmic glycogenolytic factor (glucagon). Abrahamson and Hinton [7] suggested in 1943 that the gastric mucosa was an endocrine gland. Having re-read their paper and your leading article, I wonder whether at this stage even "a little imagination" is not just too much—in linking such complex physiological activities with morbid-anatomical findings.

Christie Hospital and
Holt Radium Institute,
Manchester. M. LEVENE.

## EFFECTIVE USE OF TEACHING TIME

SIR,—In their article of March 14 Dr. Joyce and Professor Weatherall make the following statements: (1) the number of hours spent on private study did not correlate with the score in the final test; (2) the amount of time spent in reading textbooks, other references, or their own notes ranged from 0 to 21 hours per student per week.

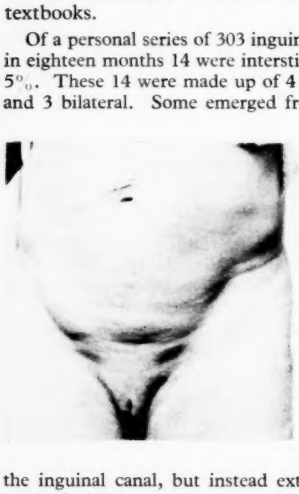
Can this be taken as evidence that all spare-time reading is useless? Were the efforts of the 21-hour student quite unrewarded? If so, I for one can think of many other ways of spending an evening, and if reading is of no value I am prepared to stop at once.

London, S.E.1. TIMOTHY CHARD.

## INTERSTITIAL INGUINAL HERNIA

SIR,—Before coming to Nigeria I thought of interstitial inguinal hernia as a rarity which one was unlikely to meet and less likely to diagnose before operation. However, in this country, where we see so many hernias of different sites and sizes, interstitial inguinal hernias, in which the sac is spread out under the external oblique aponeurosis, are fairly common; and, though they are of no particular importance, I should like to draw attention to their features, which differ from those described in my textbooks.

Of a personal series of 303 inguinal hernias operated on here in eighteen months 14 were interstitial—an incidence of nearly 5%. These 14 were made up of 4 on the right, 4 on the left, and 3 bilateral. Some emerged from the abdomen lateral to the deep epigastric vessels, others medial to them. They varied in size, the largest extending almost to the flank and costal margin. None was strangulated, and none was associated with an undescended testis; indeed, 10 out of the 14 were in females.



The characteristic feature of these interstitial inguinal hernias is that the hernia does not escape through the superficial inguinal ring from the inguinal canal, but instead extends laterally between the external oblique aponeurosis and the internal oblique muscle. Such a hernia appears therefore as a swelling in the groin above the inguinal ligament and lateral to the pubic tubercle (see figure, for which I am indebted to my colleague, Dr. M. L. Cox). If one is aware of the existence of this type of hernia, the diagnosis is usually obvious at a glance. But sometimes it may be difficult to distinguish a small interstitial inguinal hernia from the bulging of weak muscles, and diagnosis depends on feeling carefully for a definite cough impulse.

In my opinion this type of interstitial inguinal hernia is not due to a congenital sac curiously placed; after an ordinary inguinal hernia has been repaired its recurrence may be interstitial. It seems rather that a hernia which has entered the inguinal canal from the abdominal cavity is occasionally unable to escape through the superficial inguinal ring, especially in females, and instead enlarges laterally and upwards under the external oblique. Occasionally an inguinal hernia is seen which has both escaped through the superficial inguinal ring and also extended a little interstitially. The treatment of interstitial inguinal hernia does not differ from that of ordinary inguinal hernias.

Methodist Hospital,
Ituk Mbang, Uyo,
Eastern Nigeria. R. D. CUNDALL.

## HEPATIC AMŒBIASIS

SIR,—We appreciate the interest in our paper [1] shown by your annotation of Feb. 14. We feel, however, that a wrong impression may have been given and we should be grateful if you would allow us to clarify certain issues.

(1) In our paper we were at pains to point out that the term "amœbic hepatitis" is in our opinion a misnomer, and has no demonstrable pathological basis. The suggestion you mistakenly ascribe to us that "amœbic hepatitis and amœbic abscess differ only in degree" was a direct quotation from a current textbook of medicine.[2] We used this quotation in our paper to illustrate the discrepancy between the clinician and the pathologist in their concepts of hepatic amœbiasis.

(2) From our studies we concluded that the clinical entity traditionally described as amœbic hepatitis probably represents one or more deep-seated abscesses of small dimensions resolving on specific therapy without recourse to aspiration.

(3) Your annotation fails to draw attention to our observation that it was *only the smaller abscesses* which responded promptly and strikingly to specific therapy alone.

King Edward VIII Hospital,
Durban. N. McE. LAMONT
N. R. POOLER.

## STREPTOKINASE IN CHRONIC BRONCHITIS

SIR,—Many bronchitics find great difficulty in coughing up their sputum owing to its stickiness. The commonly used expectorants are valuable in stimulating cough and bronchial secretion but have little or no effect on the viscosity of the sputum.

I have recently been using a preparation of streptokinase given in tablet form which seems to have had a remarkable effect in reducing the tenacity of sputum.

The tablets, each containing 10,000 units of streptokinase and 2500 units of streptodornase, were given to three chronic bronchitics who complained of very sticky sputum, the patients being instructed to suck one tablet three or four times daily. All three patients, who had previously been taking compound sodium chloride mixture, *B.N.F.* in hot water twice daily, reported considerable reduction in the stickiness of their sputum and consequent relief from episodes of severe and distressing coughing and straining in order to bring up masses of thick mucoid phlegm.

The subjective results in these few patients have impressed me with the value of orally absorbed streptokinase in selected cases of chronic bronchitis.

London, N.W.2. D. S. NACHSHEN.

7. Abrahamson, R. H., Hinton, J. W. *Surg. Gynec. Obstet.* 1943, **76**, 147.

1. *Quart. J. Med.* 1958, **27**, 389.
2. Harrison, T. R. Principles of Internal Medicine; p. 1137. New York, 1954.

## SERUM-TRANSAMINASE LEVELS

SIR,—The methods of Cabaud et al.[1 2] for estimating serum-transaminase have two advantages: the catalytic conversion of oxaloacetate to pyruvate rather than reliance on an assumed factor, and the added specificity due to the relative insolubility of the 2:4 dinitrophenylhydrazone of α-ketoglutaric acid in toluene.

The units parallel the spectrophotometric units in the normal range[1 2] and are as convenient as any. Incubation is at "room temperature, about 26°C" and 25°C is convenient: the units cannot be compared directly with those based on 37°C incubation. We have found it better to use 0·1 ml. volume rather than rely on "1 drop" for the trichloracetic acid and aniline-citrate reagents. The buffer calls for "potassium monophosphate", and this is di-potassium monohydrogen phosphate.

Is it too late to revise the terminology? It is conventional to name enzymes according to the substrate, and glutamic acid and pyruvic acid are, in vitro, the end-products. The reaction is reversible in vivo, and I submit that to name both aminoacids gives a clearer picture of the reactions. "Glutamic oxaloacetic" becomes aspartic glutamic. This nomenclature was used by earlier workers,[3] and its general adoption seems desirable.

Group Laboratory,
St. James' Hospital,
London, S.W.12. J. KEITH CARTER.

## PIGMENTATION OF GASTROINTESTINAL MUSCLE

SIR,—In their article of Feb. 14 on Gastrointestinal Protein Loss in Idiopathic (Hypercatabolic) Hypoproteinæmia, Dr. M. Schwartz and Dr. S. Jarnum record the finding of jejunal pigmentation in three of their cases. This pigmentation, which is attributed to a lipofuscin or lipochrome, has been described previously in several conditions including "idiopathic" hypoproteinæmia, sprue, idiopathic steatorrhœa, and Whipple's disease.[1–5] Recently I have observed similar pigmentation in sixteen cases. With one exception in which the biopsy was taken from the ileum, pigmentation was always present in the jejunal muscle. In several cases, however, other parts of the gastrointestinal muscle were involved. Brown discoloration was visible to the naked eye at operation or post mortem in six instances.

The cases fall into two main groups:

1. Five cases of idiopathic steatorrhœa, four cases of jejunal diverticulosis, and one case of Whipple's disease. Steatorrhœa was proven in all of these cases. The plasma-protein levels, especially the albumin level, were frequently below normal.

2. Two cases with hiatus hernia and œsophageal ulceration; two cases with duodenal ulceration and pyloric stenosis; one case in which partial gastrectomy had been performed for a gastric ulcer; one case with an obstructive lesion of the duodenum of unknown ætiology.

In the second group the patients each had a lesion of the upper gastrointestinal tract. Steatorrhœa was not known to be present in these cases and estimations of the plasma-proteins had not been done. However, there was nothing in the recorded histories to suggest that steatorrhœa and/or hypoproteinæmia were present in any severe degree.

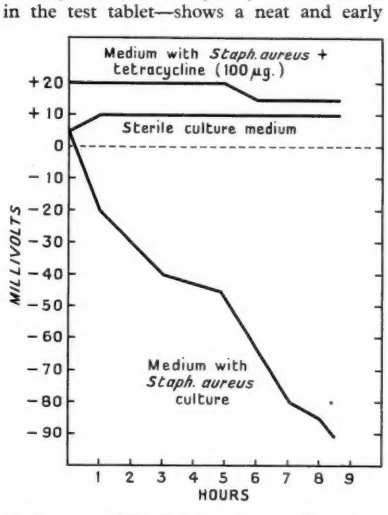
My purpose in writing this letter is to draw attention to the occurrence of pigmentation of the gastrointestinal muscle, especially of the jejunum, in cases of steatorrhœa due to jejunal diverticulosis and in a group of cases with obstructive lesions of the upper gastrointestinal tract. The nature and cause of the pigmentation and its relationship to states of nutritional deficiency and hypoproteinæmia are clearly of considerable interest and require further investigation, on which I am at present engaged.

Department of Pathology,
The Radcliffe Infirmary,
Oxford. W. C. D. RICHARDS.

## QUANTITATIVE ANTIBIOTIC SENSITIVITY TESTS

SIR,—With reference to your annotation of Dec. 27 I thought your readers might be interested in the quantitative application of a new technique for testing antibiotic sensitivity. Departing from the almost classical plate technique, I started to use the measurement of redox potentials for this purpose.[1 2] This method has been subjected to thorough trials with *Escherichia coli*, coliform organisms, *Proteus vulgaris*, and *Pseudomonas pyocyanea*. It has proved a reliable and faster method than the plate technique. Its accuracy was tested by using an antibiotic in amounts varying from 100 μg. to 1000 μg.

Since 100 μg. tetracycline ('Achromycin')—the standard amount present in the test tablet—shows a neat and early distinguishable tracing from that of the control (i.e., pure culture, without antibiotic) and since many tracings vary distinctly according to the amount of the antibiotic, the interest of this method with regard to your annotation becomes obvious. It is applicable also to penicillin. Naturally the effective doses of penicillin are much higher than the concentration of penicillin in these test tablets, because *Esch. coli* is primarily a penicillin-resistant organism.




**Redox potentials: *Staph. aureus* and tetracycline.**

When *Esch. coli* is used as a test organism the redox-potential curve corresponds fairly closely to the growth curves of Muller.[3] The advantage of this is important in evaluating the efficacy of antibiotics against this organism. Unfortunately the same is not true of staphylococci, where no such conclusion can be worked out.[3 4] The application of the test to the cocci is at present under investigation. The accompanying figure shows the results of such an experiment. Improvements have lately been made enabling the organisms (*Staphylococcus aureus*) to produce the same fall in redox potential in less than a quarter of the time. No antibiotics have yet been tested with this improved technique.

With an automatic recording apparatus which I have recently designed, the organisms under test write their own diagnosis, so to speak, in three to four hours. Is greater accuracy and speed needed? Continuous record-

1. Cabaud, P., Leeper, R., Wróblewski, F. *Amer. J. clin. Path.* 1956, **26**, 1101.
2. Wróblewski, F., Cabaud, P. *ibid.* 1957, **27**, 235.
3. Tonhazy, N. E., White, N. G., Umbreit, W. W. *Arch. Biochem.* 1950, **28**, 36.
4. Pappenheimer, A. M., Victor, J. *Amer. J. Path.* 1946, **22**, 395.
5. Aldersberg, D., Schein, J. *J. Amer. med. Ass.* 1947, **134**, 1459.
6. Paulley, J. W. *Brit. med. J.* 1954, ii, 1318.
7. Ansanelli, V., Lane, N. *Ann. Surg.* 1957, **146**, 117.
8. Gresham, G. A., Cruickshank, J. G. *Nature, Lond.* 1958, **181**, 539.

1. Zador, S. *J. clin. Path.* 1958, **11**, 278.
2. Zador, S. *ibid.* p. 339.
3. Zador, S. Unpublished results.
4. Hewitt, L. F. Oxidation-reduction Potentials in Bacteriology and Biochemistry; p. 120. Edinburgh, 1950.

ing is an additional gain; it enables the pathologist to see how the organisms react to the antibiotic from the very beginning right up to the end of the test.

This quantitative test seems a big advance on the plate technique and is, I suggest, worth further investigation.

West London Hospital Medical School (Research Department), London, W.6. S. ZADOR.

## REINFUSION OF ASCITIC FLUID

SIR,—Some 25 years ago I was asked to see a patient with ascites and hepatic cirrhosis.

At that time my colleague, the late Norman Burgess, was employing autohæmotherapy in the treatment of certain skin diseases. I withdrew several litres of ascitic fluid from this patient, and then gave an intramuscular injection of his own ascitic fluid into the buttock. A profuse diuresis followed. Three weeks later I withdrew a small amount of ascitic fluid, and again gave an intramuscular injection of 1 ml. of his own ascitic fluid. I followed up this patient for another three years until he left the district; he remained well, and no further ascites developed.

This experience seems to confirm the observation of Dr. Pálos and Dr. Antalóczy (March 7) that the reintroduction of ascitic fluid is not substitution therapy but a stimulus.

Bristol. FRANK BODMAN.

## PELVIC TUBERCULOSIS ASSOCIATED WITH INCREASED 17-KETOSTEROIDS

SIR,—In 1957 O'Donovan [1] reported the cases of 3 women in whom pelvic tuberculosis was associated with hirsutism and increased excretion of 17-ketosteroids.

In 1 case the hirsutism regressed after antituberculous therapy, while in another the hirsutism was apparently completely cured by unilateral adrenalectomy without treating the tuberculosis. In 2 cases the raised 17-ketosteroid levels were significantly depressed following the administration of cortisone. O'Donovan also cited a further case, in which pelvic endometriosis was associated with hirsutism. The evidence in these cases thus suggested that the virilisation was due to adrenal overactivity, for which chronic pelvic disease was in some way responsible.

Like O'Donovan, we have been unable to find any published mention of the association, and, in view of its obvious importance in the differential diagnosis of primary adrenal hyperplasia, we report here a case in a Bantu, in whom pelvic tuberculosis was associated with increased excretion of neutral 17-ketosteroids which could be depressed by cortisone. Hirsutism, was, however, absent.

The patient, aged 25, presented in January, 1957, with primary amenorrhœa. Her past and family history were negative. Apart from the finding of a small uterus (internal length 2 in.), examination revealed no abnormality. Diagnostic curettage failed to produce a specimen of endometrium.

On endocrinological investigation the only significant findings were the raised 24-hour urinary excretions of neutral 17-ketosteroids, which, following the administration of cortisone (100 mg. intramuscularly daily for 8 days), fell notably. Before cortisone the level was 14·9 mg. (method of the Medical Research Council Committee on Clinical Endocrinology [2]). This figure is high for a Bantu woman. Immediately after cortisone it fell to 4·6 mg., while 11 days later it rose to 20·8 mg. The test was repeated 2 weeks later with values of 19·0, 5·7, and 14·9 mg. respectively.

At laparotomy (2 weeks after the end of the second course of cortisone) the right ovary, both fallopian tubes, and the pelvic peritoneum were found to be extensively involved by old fibrocaseous tuberculosis. The left ovary was normal and contained a corpus luteum as well as corpora albicantia and corpora atretica. In neither ovary was there evidence of theca-cell or hilus-cell hyperplasia. The uterus was small and bicornuate, and curettings on this occasion revealed the typical features of endometrial tuberculosis. The adrenals were macroscopically normal. Biopsy of the left adrenal showed some relative increase in the depth of the zona glomerulosa, the cells of which were much vacuolated. The zona fasciculata and zona reticularis were normal. The liver was macroscopically and microscopically normal.

While on the basis of O'Donovan's findings it would seem reasonable to postulate that chronic pelvic disease may be causally related to adrenal overproduction of androgens, the mechanism of this remains obscure. A considerable literature testifies to the close functional relationships between the adrenals and the gonads [3]; in particular there is evidence, both in humans and in animals, that ablation or cessation of ovarian function may be followed by excessive secretion of adrenal androgens,[4 5] and it would be tempting to explain the action of chronic pelvic disease in terms of a suppressive effect on ovarian function. In our case, however, one of the ovaries appeared normal, and it is generally agreed that a single ovary is capable of maintaining adequate ovarian function. The absence of hirsutism also remains unexplained, but this may be related to the lack of hairiness in the Bantu. Lewis [6] has noted that the Negroes of the West Coast of Africa are quite glabrous.

Baragwanath Hospital, Johannesburg, South Africa. H. C. SEFTEL
B. M. BLOOMBERG.

## RADIOGRAPHS REPRODUCED AS LANTERN-SLIDES

SIR,—Many clinicians and radiologists wish to keep a permanent record of interesting and instructive radiographs, but are deterred by the lack of the services of a medical photographer. The high cost of professional work (about 5*s.* for a 2×2 in. slide) may prevent the acquisition of a private collection. A reversal film is now available that allows the amateur photographer to make high-quality 2×2 in. (5×5 cm.) slides for about 6*d.* each.

The radiograph is put up on a standard X-ray viewing-box, and unwanted parts are screened-off with cardboard. A 35 mm. camera, with a removable lens to allow the interposition of an extension tube or close-focusing mount is necessary, as focusing to within 12 in. (30 cm.) of the radiograph is sometimes desirable. In practice most radiographs are suitably photographed at a distance of 2–3 ft. Alternatively, a telescopic-type lens may be used. A rigid camera stand is desirable. Focusing is aided by affixing a paper-clip to the centre of the radiograph with ' Sellotape ', taking care to remove this before exposing the film.

Exposure may be calculated using an exposure meter held 6–9 in. from the illuminated radiograph, the reading being taken from the part of greatest interest. Where a wide-density range is present a mean reading is taken. So wide is the exposure latitude of the reversal film, however, that with experience the exposure meter may be dispensed with. Using, for example, a fixed-time exposure of $^1/_8$ sec. diaphragm settings of *f*3·5–6 will be suitable for most radiographs. Underexposure (e.g., *f*8–11) will often accentuate contrast over the middle density ranges.

Processing is by the manufacturer, a roll of 36 " negative " tranparencies being returned (i.e., as the original radiograph appeared), and no further printing is necessary. The eventual cost of the completed slide depends largely on the quality of mount and glass used. If more than one copy is required, several frames should be exposed in the first instance.

The reversal film has great practical advantages over the conventional two-stage method involving printing on to lantern

1. O'Donovan, D. K. *Lancet*, 1957, ii 803.
2. *ibid.* 1951, ii, 585.
3. Jones, I. C. The Adrenal Cortex; p. 99. London, 1957.
4. Hertz, R. *Rec. Prog. Horm. Res.* 1950, **5**, 401.
5. Woolley, G. W. *ibid.* p. 383.
6. Lewis, J. H. The Biology of the Negro; p. 63. Chicago, 1942.

plates, and may eventually supersede it. A radiograph viewed by transmitted light has a very great density range (of the order of 1–1000). Photographic paper and lantern-plate emulsions cannot reproduce this, and " telescopes " the range so that fine degrees of contrast by which certain shadows are appreciated are lost (e.g., the shadow of a hiatus hernia behind the heart shadow in a plain posteroanterior chest radiograph). The skilled photographer can allow for this in showing certain densities to best advantage, but the overall effect may still be unsatisfactory. The reversal film, on the other hand, has a much greater density range, and is particularly useful in the middle ranges. This film is panchromatic, as opposed to lantern plates, which are monochromatic, and the emulsion contains an anti-halation layer.

We have made over 300 slides of radiographs by this method, and the contrast and definition have been found suitable for all types of work, including fine bone detail. Comparison in certain instances with conventional professionally produced slides has endorsed this opinion. The method can also be used to make slides of diagrams, tables, &c., for illustrating lectures.

We are grateful to Messrs. Gevaert Ltd. for technical information about their ' Dia-direct 26 Pan Reversal ' miniature film.

E. A. W. HOUGHTON
F. G. M. ROSS.

Royal Infirmary, Bristol.

## ANTIBIOTICS AND THE COMMON COLD

SIR,—Dr. Ritchie (Jan. 24) has ably defended his use of antibiotics in the treatment of the common cold. Having been employing " lower-than-conventional " doses of certain antibiotics for ten years for purposes including prophylaxis and treatment of the common cold,[2] I should like to elaborate on some points.

Professor Garrod's suggestion (Jan. 3) that, if antibiotics are to be used at all, penicillin is the choice would seem fortified by Dr. Wood's demonstration (Jan. 31) that there were as many penicillin-sensitive as tetracycline-sensitive oropharyngeal bacteria. Other factors, however, are involved.

Antibiotics are used in infections because they are bacteriostatic and/or bactericidal. But is this their sole mode of action? Extensive studies on the pharyngeal flora of rheumatic-fever subjects where sustained antibiotic administration was directed against supposedly sensitising streptococci show that after several months those organisms still extant have become resistant to the particular antibiotic chosen to eradicate them. In mucoviscidiosis, where sustained administration of chlortetracycline proved to be a therapeutic triumph, no essential difference is found between the before-and-after pharyngeal flora.[3] Acne vulgaris is controlled only while 'mycins are continually exhibited,[4] yet one has as little difficulty in finding staphylococci on the skin of the controlled acne subject as in the lesions initiating antibiotic treatment.

Some years back, Mosonyi et al.[5] pointed out that streptomycin administration frequently benefited patients whose illness was not due to streptomycin-sensitive organisms. This, as well as my own reports on antibiotics in non-infectious " adaptation " diseases, finally led to your own editorial comment [6] that inexplicable therapeutic effects were forthcoming from antibiotics even where an infective agent, in the classic sense, might be absent. The common cold is decidedly initiated by an infective agent but one which is quite invulnerable to antibiotics in use. I am informed that, since the introduction of antibiotics into poultry husbandry such viral conditions as new-duck disease and chicken leucoses have sharply declined.

Penicillin has become an increasingly dangerous drug. With a yearly death-toll of almost 40 in this city certified by the medical examiner's offices as due to penicillin reaction, I justify the opposition I have voiced against indiscriminate penicillin administration in this locality for the past ten years, during which I have specifically incriminated penicillin for the induction of acute leukæmia.[7] At one large municipal hospital that I serve as clinical pathologist, the penicillin-reaction rate on some surgical wards was over 10% before I secured rescinding of the standing order for administration of penicillin to all surgical patients.

We are beginning to see acute leukæmia with some frequency among Negro children, whereas ten years ago this was a rarity. A recent study [8] from the National Health Institute has confirmed the thesis that the leukæmic child is an " allergic reactor " [9]; there is a significantly higher prevalence of familial and personal allergy in children who develop leukæmia and malignant lymphoma. Based on a suggested relationship between propensity to call the doctor and the incidence of childhood leukæmia in certain population groups in the New York area,[10] a study of possible iatrogenesis of leukæmia is under way.[11]

Dr. Ritchie waived trial of streptomycin in his study because, a priori, the pharyngeal flora could not be affected. But I employed oral streptomycin in dosages of the same order as those of tetracyclines used by Dr. Ritchie, and it was quite effective.

We must be concerned about the emergence of resistant pathogens as a hazard of widespread antibiotic usage; and no disease is as widespread as the common cold. Many physicians—probably the majority of general physicians in this country—prescribe an antibiotic or sulphonamide, often by telephone, when a cold impends or is extant. Until the advent of the " broad-spectrum " antibiotic, when everyone having a cold felt that they were entitled to treatment by one of these, a physician was frequently called to the home, not to examine, diagnose, and advise, but to hear the mother say that " Johnny has a cold—I want him to have a shot of penicillin ".

My experience fully confirms the results reported by Dr. Ritchie.

Jamaica, New York. ROBERT D. BARNARD.

## ALDOSTERONE EXCRETION IN NORMAL PREGNANCY AND PRE-ECLAMPSIA

SIR,—It is hard to follow the reasoning in the hypothesis advanced by Dr. Kumar and his colleagues (March 14). On the one hand, they hold that aldosterone removes sodium from muscle cells, thereby lowering the intracellular sodium values in normal pregnancy (as compared to the non-pregnant state); and then they suggest that in normal pregnancy there exists in the placenta another substance with like properties capable of lowering the intracellualr sodium as well—the cell-sodium-lowering factor whose activity wanes when the placenta becomes ischæmic in toxæmia. On the other hand, they state that " if there exists a ' cell-sodium-lowering (C.S.L.) factor' in pregnancy then a compensatory rise in aldosterone would probably be harmless only as long as this factor remained ". Their search for an explanation of their data has forced them into this dilemma.

Were their ætiological argument sound it would have explained equally their data in normal *and* in toxæmic pregnancy—which a little reflection shows it does not. Once again an ætiological hypothesis of pre-eclampsia based on the placenta is found unacceptable.

London, W.1. JOHN SOPHIAN.

1. Ritchie, J. M. *Lancet*, 1958, i, 618.
2. Barnard, R. D. *N.Y. Physician*, 1951, **36**, 73.
3. Shwachman, H. *Pediatrics*, 1951, **7**, 153.
4. Barnard, R. D. *N.Y. St. J. Med.* 1952, **52**, 1528.
5. Mosonyi, L., Juthasz, J., Pollák, L., Zulik, R. *Lancet*, 1951, ii, 81.
6. *ibid.* 1952, ii, 375.
7. Barnard, R. D., Fox, H. L. *N.Y. St. J. Med.* 1953, **53**, 2826.
8. Manning, M. D., Carroll, B. E. *J. nat. Cancer Inst.* 1957, **19**, 1087.
9. Barnard, R. D. *N.Y. St. J. Med.* 1947, **47**, 2703.
10. Lilienfeld, A. M. *Publ. Hlth Rep., Wash.* 1959, **74**, 29.
11. Personal Communication from the Director, Cancer Control and Research Division, New York City Department of Health.

# Parliament

### What is an "Invalid"?

ON March 18, in the House of Lords, LORD AMULREE asked the Government for their interpretation of the word "invalid," particularly in relation to elderly sick. He asked, he said, because under the National Assistance Act and the National Health Service Act difficulties could arise in allocating responsibility between the health department and the welfare department of the local authority. For instance, in his view the local authority might determine that a recommendation for a domiciliary meal should be dealt with by the welfare department and that an old person required a meal under a health-department grant only if he had some specific condition needing a specific diet. In London a voluntary organisation, called Invalid Meals for London, supplied meals on a medical certificate for either special diets or a well-balanced general invalid diet. The London County Council made a substantial grant towards the organisation's fund, and accepted medical certificates whether for patients with specific conditions or for people who needed the general invalid meal. Other authorities would give a grant only for special diets ordered for specific conditions. Surely people who were confined to their house, which implied some degree of invalidism, should be the responsibility of the health department where their proper nutrition could be regarded as part of their medical treatment.

The Earl of ONSLOW said that, though the word "invalid" was not actually used in the National Health Service Act, domiciliary services could be provided by local authorities for the prevention of illness and the care and aftercare of persons suffering from illness. In his view these powers included giving financial support to voluntary organisations supplying domiciliary invalid meals. But it was the business of the local health authorities to decide what assistance they would give.

### Education Estimates

THE Ministry of Education estimates for 1959–60 show a decrease of £276½ million, for much of the money to be spent on schools will now reach local authorities through the Ministry of Housing and Local Government as part of the block grant. The estimate for universities and colleges rises by just under £8 million to a total of £58 million.

# Public Health

### Radiostrontium and Radiocæsium in Drinking-water

THE fallout of radiostrontium and radiocæsium in rain has been measured in Britain since 1954, but not much was known about its effects on the public drinking-water supplies. The Atomic Energy Research Establishment at Harwell has now published[1] the results of some preliminary investigations which show how these radioactive isotopes have penetrated into certain selected public supplies, how they have varied with the type of source (lake, river, or well), and the relation of drinking-water to other food in ingestion of radiostrontium and radiocæsium.

Tests were made between September, 1957, and June, 1958, of lake waters used by seven large areas of population—Liverpool, Manchester, Leeds, Birmingham, Cardiff, Glasgow, and mid-Northamptonshire. The mean level of $^{90}Sr$ in these waters was 0·45 $\mu\mu$C per litre, which represented about 15% of the content of rain water at that time. There were differing ratios between $^{89}Sr$ and $^{90}Sr$ which reflected the effect of reservoir storage on the age of the water.

River sources supplying Coventry, Oxford, and London were found to have a mean $^{90}Sr$ content of 0·24 $\mu\mu$C per litre (about 10% of that of the rain), with wide variations due to the inconsistent components of river waters.

Well waters used by Wolverhampton, Cambridge, and Brighton had very low values for $^{90}Sr$—less than 0·01 $\mu\mu$C per litre—and in none did the value exceed 1% of that in rain. $^{137}Cs$ did not seem to have penetrated from rain into these sources of drinking-water as much as had $^{90}Sr$. The highest level of cæsium was found in river waters.

Assuming that an ordinary individual drinks 1·5 litres of water daily in various guises, these lake and river waters would contribute only an extra 10% of $^{90}Sr$ to the diet, and the effect of the well waters would be negligible.

Investigations of this kind are most welcome. Water undertakers, public-health authorities, and the medical profession as a whole need to learn a lot more about the ways and rate of change in the human environment.

1. A.E.R.E., Harwell: A Preliminary Survey of Radiostrontium and Radiocæsium in Drinking Water in the United Kingdom. H.M. Stationery Office. 1959. Pp. 11. 2*s*. 6*d*.

### Smallpox in Liverpool

SMALLPOX was diagnosed last week [1] in a medical technician, one of the contacts of the Liverpool medical student now recovering from the disease.[2] He had been under observation and was vaccinated on March 9. He became ill on March 17 and a prodromal rash appeared next day. On March 19 a second medical student was isolated because he had a rash, which was possibly no more than a reaction to vaccination.

# Obituary

### ERNEST HERRMANN RINK

B.M. Oxon., F.F.A. R.C.S., D.A.

Dr. E. H. Rink, consultant anæsthetist to Guy's Hospital, London, died on March 6 at the age of 54.

He was educated at Tonbridge School and Magdalen College, Oxford, and Guy's Hospital. After qualifying in 1930 he held several house appointments at Guy's. It was then the custom for many of the anæsthetics to be given by the house-surgeons and house-physicians, and it was this part of his duties which aroused Rink's interest in the subject. In 1933 he became a demonstrator in anæsthesia and in the following year one of the first resident anæsthetists appointed at Guy's. In 1935 he obtained the newly instituted diploma of anæsthetics, and the same year he was appointed to the consultant staff of the hospital.

During the late war he served with the R.A.M.C. in the Middle East as an anæsthetic specialist and as adviser in anæsthetics to 21 Army Group in North West Europe. He returned to Guy's on demobilisation and became increasingly interested in anæsthesia for intrathoracic procedures. Many ex-Service registrars owe to him their preliminary tuition in this branch of the specialty. He was elected F.F.A. R.C.S. in 1948.

P. J. H. writes:

"James Rink was a man with many interests. He was passionately fond of music and the opera, a feeling which he shared with his family. Sport, particularly tennis and cricket, had their place, and he was so widely read that there were few subjects on which he could not converse on equal terms with his colleagues. He will long be remembered as the centre of many lively discussions in the staff common room. His standards of professional honesty were high. He was his own most severe critic, but a junior could turn to him at any time for advice, knowing that he would receive the full benefit of Rink's profound knowledge of his specialty. He was always kind and would go to a great deal of trouble and inconvenience on behalf of a colleague if he thought he could be of help.

"He will be remembered for the work he did during the early stages of the development of cardiac surgery at Guy's Hospital. When, on the advice of his physicians, he reluctantly had to give this up he maintained his keen interest in the subject. During the latter years of life he struggled against increasing ill-health, but he always remained cheerful, and even when obviously far from well, he produced typical penetrating shafts of wit which delighted his friends".

Dr. Rink leaves a widow and two sons.

1. *Liverpool Daily Post*, March 19 and 20.
2. *Lancet*, March 21, 1959, p. 638.

### Mr. W. J. STUART

D. G. writes:

"For sixteen years 'Pussy' Stuart filled, with great acceptance, the position of honorary secretary to the Aesculapian Club, the dining-club founded in Edinburgh by Dr. Andrew Duncan in 1773, consisting of 'twenty-two members chosen from among the Fellows of the Colleges of Physicians and Surgeons'. A few years ago he published a delightful *History of the Aesculapian Club* which is a model of elegant prose and clear description. Probably his keen interest in the classics and in history aided his facility of expression, and he was an active member of the Classical Association of Scotland and the first vice-president of the Scottish Society of the History of Medicine. Many will remember his splendid and well-phrased Harveian oration on *Harvey and Integration* in 1936 at the annual festival of the Harveian Society of Edinburgh.

"Men of his calibre are few, and he is greatly missed. Throughout his career of continual helpfulness to others he won a high place as surgeon and teacher, as scholar and as orator, but his friends will choose to remember him as the gentlest and kindest of men, and as one whose serene spirit and singleness of purpose brought happiness to all who were privileged to know him."

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We record with regret the death of Mr. J. M. WILLIAMS, who worked for *The Lancet*, as printer's reader, for 52 years. He joined us well before the turn of the century, when the journal was set in type by our own staff at our office in the Strand; and 29 years later, when our printing was transferred to Messrs. Hazell, Watson & Viney, he moved to Long Acre to continue the same work. A good reader can be a great help both to editors and to contributors, and Mr. Williams was a very good one. He acquired much knowledge; he was carefully accurate without being pedantic; and as head reader he was a friend from whom all the editorial staff were glad to learn. He retired in 1944.

## Appointments

CHAPLAIN, WILLIAM, M.B. St. And.: senior assistant psychiatrist to be designated deputy physician-superintendent, Aston Hall Hospital, Aston-on-Trent.
CHRISTISON, DAVID, M.B. Glasg., D.O.M.S.: consultant ophthalmologist, Glasgow Eye Infirmary.
CLARKE-WILLIAMS, M. J., M.B. Cantab.: assistant physician in geriatrics, Ipswich and East Suffolk Hospital group.
EVANS, D. L., M.A. Cantab., F.R.C.S.: consultant orthopædic surgeon, Westminster Hospital, London.
FOX, A. D., M.B. Lond., D.O.: ophthalmologist, children's refraction clinics, Ongar, Epping, and Waltham Abbey, Essex.
HARDY, HARRY, M.B. Sheff., D.O.: consultant ophthalmic surgeon, Ipswich and East Suffolk Hospital Group.
OWEN, ROBERT, M.B. Lond., M.CH. ORTH. Lpool, F.R.C.S.: consultant traumatic and orthopædic surgeon, Clwyd and Deeside H.M.C.
PILLAI, SUNDRAM, M.B. Rangoon, F.R.C.S., D.O.M.S., D.L.O.: consultant ophthalmologist, Mid-Glamorgan H.M.C.

**Newcastle Regional Hospital Board:**

FOREMAN, A. G., F.R.C.S.E.: senior casualty officer, South East Northumberland group of hospitals.
NEWTON, D. R. L., M.R.C.P., D.PHYS.MED.: consultant physician in physical medicine, North and South Tees-side, Darlington, and Northallerton groups of hospitals.
WEBSTER, D. D., M.B. Durh., D.P.M.: consultant psychiatrist, St. Luke's Hospital, Middlesbrough.
WETHERLY, R. E., M.B., B.SC. Aberd.: assistant pathologist (S.H.M.O.), Sunderland group of hospitals.
WILSON, A. O. A., M.B. Edin.: assistant psychiatrist, Garlands Hospital, Carlisle.

**Colonial Appointments:**

BOULGER, L. R., M.B. Manc., DIPL. BACT.: specialist (pathologist), Nigeria.
CHRISTERSEN, A. J., M.B. Copenhagen: M.O., Sierra Leone.
CLIFFORD, P. P., M.CH. N.U.I., D.L.O.: surgical specialist (E.N.T.), Kenya.
ENDE, R. O. E., M.D. Freiburg: specialist (pathologist), Eastern Region of Nigeria.
FARR, A. G., M.B.E., M.B. Cantab., D.P.H., D.T.M. & H., D.I.H.: senior M.O., Aden.
FAWKES, M. A., M.B. Cantab., D.P.H., D.T.M. & H.: senior health officer, Nigeria.
GROUND, K. E. A. U., M.R.C.S, D.T.M. & H.: senior M.O. (training), Uganda.
HABIB, G. G., M.B. Birm.: M.O., Trinidad.
HARDY, JOAN, M.B. Cantab.: specialist pathologist (blood transfusion), Nigeria.
KONFORTION, PAUL, M.B. Lond.: M.O., Mauritius.
LAUFER, IZYDOR, M.D. Parma, D.P.H.: senior M.O., Tanganyika.
MCGUINNESS, W. J., M.B. St. And.: medical superintendent, Tanganyika.
MARK, A. W., M.B. Manc.: M.O., Sierra Leone.

## Notes and News

### SILVER JUBILEE AT OXFORD

SCIENCE and the arts appropriately joined forces to celebrate Sir Wilfrid le Gros Clark's silver jubilee as Dr. Lee's professor of anatomy, when on March 16 his portrait bust in bronze by Sir Jacob Epstein was given by his colleagues, associates, and former pupils to the University Department of Human Anatomy at the opening of its new extension.

Speaking in the new dissecting-room before a distinguished group, including Sir Jacob and Lady Epstein, the pro-vice-chancellor, university professors, and heads of colleges, Sir George Pickering, the regius professor of medicine, paid tribute to the famous past occupants of the chair, to which Sir Wilfrid's contributions in anthropology and anatomy have added lustre. The felicity of Sir Wilfrid's closely reasoned dissertation on the humility of pride made it clear why senior members of his faculty often revisit the old lecture-room (happily still preserved) at 9 A.M.—not only to learn of the latest correlation between structure and function in the nervous system but also to hear undergraduate lectures as they should be given.

The ever-increasing size of university science departments is illustrated by the hotchpotch of buildings in the main science area to the east of Parks Road in Oxford. It can be no easy task to devise a new building in harmony with such diverse styles as a replica of the abbey kitchen at Glastonbury, a classico-gothic pile, a glass-sided pseudo-yacht-club, and a few wooden huts—particularly as money is always as limited as space. But the architects of the extension to the department of human anatomy have brought it off. The dissecting-room, with its 40 ft. double-lensed glass roof, vaulted and heat-resisting, framed with continuous strip lighting and set into a lemon yellow ceiling, is memorable. On a sunny morning golden light falls on the greys and greens of the walls and floor, giving a warm light which cannot be glaring. Under the dissecting-room is a 110-seat laboratory for embryology and histology. The neurosurgical research unit is at last given the rooms it deserves, and the new offices, the photographic unit, and the animal-house are neatly fitted into the other floors. Yet the general impression is of light and space. The days, over 25 years ago, when women undergraduates were decently tucked away to dissect under the roof seem far away; but it is sad that the marble slabs, the pride of the last professor, have had to be honourably retired.

The architects of the new extension, which has cost £160,000, are Lanchester & Lodge.

### DIAGNOSIS OF TOXOPLASMOSIS

ROUTINE examination for antibodies to toxoplasma, which have hitherto been carried out by Prof. C. P. Beattie at Sheffield and Dr. I. A. B. Cathie at the Hospital for Sick Children, Great Ormond Street, London, will from April 1 be transferred to the public health laboratories at Leeds and Swansea. Specimens from hospital regions 1–4, 13, and 14 and from Scotland (i.e., North Britain down to and including the counties of Cheshire, Derby, Leicester, Huntingdon, Cambridge, and Suffolk) should be sent to Dr. G. B. Ludlam at the Public Health Laboratory, Bridle Path, York Road, Leeds, 15 (tel.: Leeds 64-5011); and specimens from hospital regions 5–12 to Dr. D. G. Fleck, at the Public Health Laboratory, Cockett Road, Swansea (tel.: Swansea 24041/2).

### NATURAL CAUSES

ON March 16, at the Arts Theatre Club, the Euthanasia Society [1] presented the Hovenden Theatre Club production of Vera Colebrook's *Natural Causes*.

The argument of the play turns on whether an old lady, who has had a stroke and does not want to live on disabled, should be given penicillin for the pneumonia of which she is dying. This problem brings out the opposing viewpoints of two

1. The address of the Society is 13, Prince of Wales Terrace, London, W.8.

doctors, and gives insight into the emotional conflicts of the patient's family. Much wisdom is lightly interjected in the charming Irish brogue of a nursing sister.

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**University of Leeds**

On May 2 the honorary degree of D.SC. will be conferred on Dr. J. E. Salk, Commonwealth professor of experimental medicine in the University of Pittsburgh.

Dr. W. K. J. Walls has been appointed lecturer in anatomy, Dr. J. M. Roberts lecturer in psychiatry, and Mr. F. G. Smiddy lecturer in surgery.

**University of Edinburgh**

On July 21, at a graduation ceremonial to be held on the occasion of the meeting in Edinburgh of the British and Canadian Medical Associations, the honorary degree of LL.D. will be conferred on Lord Adrian, Dr. Angus Macrae, Sir Arthur Thomson, Prof. C. H. Best, Prof. J. R. Lemieux, and Prof. W. G. Penfield.

Dr. Guy Boissard has been appointed lecturer in the department of bacteriology, Dr. Mary W. Moss lecturer in the general-practice teaching unit, and Dr. H. B. Torrance lecturer in the department of surgical science.

**Royal College of Surgeons of England**

Surgery lectures and clinical conferences will be held on weekdays from Monday, April 6, to Wednesday, April 22, at the college, Lincoln's Inn Fields, London, W.C.2. Further particulars may be had from the assistant secretary of the college.

**Royal College of Physicians of Edinburgh**

On Wednesday, April 15, at 5 P.M., at the college, 9, Queen Street, Edinburgh, 2, Mr. T. Holmes Sellors will give the George Alexander Gibson lecture. His subject will be the contribution of surgery to clinical cardiology.

**Royal Australasian College of Physicians**

At a meeting of the New Zealand fellows and members of the college, held in Dunedin, Feb. 18, the following were admitted to membership:

R. T. Bush, J. M. Costello, A. E. Dugdale, G. S. McL. Kellaway, A. V. Kurta, J. H. McIntyre, R. B. I. Morrison, R. G. Park, P. J. Scott, J. D. Todd, J. C. P. Williams.

**Empire Rheumatism Council**

The Council announce the award of a research fellowship to Dr. D. H. Weir and of Geigy travelling fellowships to Dr. H. Wykeham Balme and Dr. Madeline Keech.

**International Conference on Medical Electronics**

This conference will be held in Paris from Wednesday, June 24, to Saturday, June 27. The regional programme representative for Great Britain and the Commonwealth is Dr. C. N. Smyth, University College Hospital, London, W.C.1.

**Royal Society**

Though the 25 newly elected fellows of this society do not include any members of the medical profession, the work of the following is closely associated with medical research:

Dr. G. H. BEALE, senior lecturer in genetics, University of Edinburgh; Dr. FRANZ BERGEL, professor of chemistry in the University of London, at the Chester Beatty Research Institute of Cancer Research, Royal Cancer Hospital; Dr. ANN BISHOP, director of the Medical Research Council Group for Research in Chemotherapy, at the Molteno Institute of Biology and Parasitology, Cambridge; Dr. F. H. C. CRICK, member of the staff of the Medical Research Council Unit for Research on the Molecular Structure of Biological Systems at the Cavendish Laboratory, Cambridge; Dr. D. W. W. HENDERSON, director of the Ministry of Supply Microbiological Research Establishment, Porton; Dr. R. D. KEYNES, lecturer in physiology, University of Cambridge; Dr. J. F. TAIT and Mrs. SYLVIA TAIT, both now at the Worcester Foundation, Shrewsbury, Massachusetts, and formerly on the staff of the Courtauld Institute for Biochemistry, Middlesex Hospital, London; Dr. M. H. F. WILKINS, deputy director, Medical Research Council Biophysical Research Unit, at the University of London King's College.

**Institute of Diseases of the Chest, London**

Clinical demonstrations will be arranged by Dr. J. R. Bignall at the institute, Brompton Hospital, Fulham Road, S.W.3, at 5 P.M. on Fridays from April 17 to July 3. Open lectures will be held at the same time on Wednesdays from April 22 to July 1.

**British Overseas Airways Corporation**

The personnel and medical branches of B.O.A.C. are being brought together in a single department, and Dr. K. G. Bergin, at present chief medical officer, has been appointed director of personnel and medical services.

**Carlsberg-Wellcome Travelling Research Fellowships**

Applications are invited for these fellowships for 1959–60. Their object is to encourage cooperation, on an exchange basis, between Danish and British research-workers in any branch of the natural sciences which has a bearing upon human and animal medicine.

One fellowship annually is awarded to a candidate from the United Kingdom for a year's work in Denmark and one annually to a Danish candidate for a year's work in the United Kingdom. The stipend may range from £800 to £1200 per annum (or the equivalent sums in Danish kroner); travelling and some incidental expenses are provided in addition. The tenure of the awards will start in September. Further information may be had from the assistant scientific secretary of the Wellcome Trust, 52, Queen Anne Street, London, W.1. Applications must be submitted before April 30.

**Medical Teaching Centre at Cardiff**

The board of governors of the United Cardiff Hospitals and the council of the Welsh National School of Medicine are inviting architects resident in Great Britain, Northern Ireland, and Eire to take part in an open competition for designs for this new centre, which is to be erected on a site of 53 acres. It will comprise a teaching hospital of 650 beds, with a possible extension to 800 beds, a medical school, a dental hospital and school, and residential accommodation for nurses and medical students. The five assessors of the competition include the provost of the medical school (Dr. A. Trevor Jones) and Dr. A. R. Culley.

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Dr. Paul Wood will speak on modern auscultation at a meeting of the Yorkshire Thoracic Society at 5.30 P.M. in Leeds General Infirmary on Friday, April 17 (not April 10 as previously announced).

Mr. C. S. Bangay, clerk of the London executive council, retires on March 31. He joined the staff of the London insurance committee in 1913.

A microscope is needed at a progressive primary school which believes in early cultivation of scientific interest and imagination. Any reader who has a suitable microscope which he would be willing to give to the children is asked to write to Mr. D. Gwyn Williams, one of the managers of the school. His address is Room 104A, Bush House (S.W. Wing), London, W.C.2.

## Diary of the Week

MARCH 29 TO APRIL 4

**Tuesday, 31st**

ROYAL ARMY MEDICAL COLLEGE, Millbank, S.W.1
5 P.M. Brigadier R. R. Bomford: Essentials of Diabetic Management.

ROYAL STATISTICAL SOCIETY
5.30 P.M. (London School of Hygiene and Tropical Medicine, Keppel Street, W.C.1.) *Medical Section.* Mr. W. Z. Billewicz: Maternal Height and Childbearing Performance.

**Wednesday, 1st**

ROYAL SOCIETY OF MEDICINE, 1, Wimpole Street, W.1
5.15 P.M. *History of Medicine.* Dr. W. S. C. Copeman: Medical Education in Tudor Times.

ROYAL INSTITUTE OF PUBLIC HEALTH AND HYGIENE, 82, Portland Place, W.1
3.30 P.M. Dr. Israel Gordon: Old People's Flats.

**Thursday, 2nd**

ROYAL SOCIETY OF MEDICINE
8 P.M. *Neurology.* Dr. J. Benassy (Paris), Dr. J. B. Cook, Dr. A. G. Hardy: Current Views on Spinal Injuries.

ALFRED ADLER MEDICAL SOCIETY
8.15 P.M. (1, Wimpole Street, W.1.) Dr. E. K. Lederman: Existential Psychotherapy.

**Friday, 3rd**

ROYAL SOCIETY OF MEDICINE
5.30 P.M. *Anæsthetics.* Dr. Philip Hugh-Jones: Respiratory Function Tests.

INSTITUTE OF LARYNGOLOGY AND OTOLOGY, 330, Gray's Inn Road, W.C.1.
3.30 P.M. Dr. Isaac Friedmann: Recent Advances in Chemotherapy.